June 11, 2012

David Campana, R.Ph.
Montana Department of Public Health & Human Services
111 North Sanders Street
Helena, Montana 59620

Dear Mr. Campana:

Your Sr Account Director-Regional, Alan Garber, has forwarded your request regarding BRILINTA® (ticagrelor) Tablets. The following information is being provided, as a professional courtesy, in response to your request:

BRILINTA AMCP Dossier

The information provided is confidential business information of AstraZeneca. This information should not be disclosed to any other party other than those involved in this specific medical inquiry without the prior written consent of AstraZeneca.

These materials may include information that is not found in the currently approved prescribing information for BRILINTA. The enclosed information is intended to provide pertinent data in response to your request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for BRILINTA. The prescribing information for this product contains a boxed warning(s). Please consult the warning section of the prescribing information for further details and other important safety information. Prescription drugs used in a manner other than their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. Prescribing information for BRILINTA may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.

Thank you for your interest in BRILINTA. If we may be of further assistance to you, please contact AstraZeneca at 1-877-893-1510.

Tel 877 893 1510
Fax 302 885-1400
www.astrazeneca-us.com

Medical Resources FOC/CE1 706, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437

Sincerely,

Laurie Mohler, R.Ph., CGP, FASCP
Sr. Medical Information Manager

00009674

BRILINTA®

(ticagrelor)

Formulary

Submission Dossier

Provided by

U.S. Medical Information

&

Health Economics and Outcomes Research

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These materials may include information that is not found in the currently approved prescribing information for BRILINTA®. The enclosed information is intended to provide pertinent data in response to your request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for BRILINTA®.

For further medical information inquiries, please contact AstraZeneca Medical Affairs at 1-877-893-1510.

AstraZeneca

TABLE OF CONTENTS

Abbreviations

ACC=American College of Cardiology
ACCF=American College of Cardiology Foundation
ACE-I=angiotensin-converting enzyme inhibitor
ACS=acute coronary syndrome
ADP=adenosine diphosphate
AE(s)=adverse event(s)
AHA=American Heart Association
AHFS=American Hospital Formulary Service
ARB=angiotensin receptor blocker
ARR=absolute risk reduction
ASA=acetyl salicylic acid
AUC=area under the plasma concentration-time curve
$AUC_{0-\infty}$=area under the plasma concentration-time curve from 0 to infinity
AUC_{0-8}=area under the plasma concentration-time curve over 8 hours
$AUC_{0,t}$=area under the plasma concentration-time curve within the dosing interval
AV=atrioventricular
BIM=budget impact model
BMI=body mass index
BMS=bare metal stent
BNP=N-terminal pro-brain natriuretic peptide
BP=blood pressure
CABG=coronary artery bypass graft
CAD=coronary artery disease
cECG=continuous electrocardiography
CHF=congestive heart failure
CI=confidence interval
CKD=chronic kidney disease
CL/F=total plasma oral clearance
CL/*F*=apparent plasma clearance
CLP=clopidogrel
C_{max}=maximum plasma concentration
CK-MB=MB isoenzyme of creatine kinase
COMMIT=Clopidogrel and Metoprolol in Myocardial Infarction
COPD=chronic obstructive pulmonary disease
CPI=Consumer Price Index
CPT=Current Procedural Terminology
CrCL=creatinine clearance
CRP=C-reactive protein
CURE=Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV=cardiovascular
CYP=cytochrome P450
DISPERSE=The Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction
D/C=discontinuation
DES=drug-eluting stent
DLCO=single-breath diffusion lung capacity measured by using carbon monoxide
DM=diabetes mellitus
DRG=diagnosis-related group
EC=enteric-coated
ECG=electrocardiogram
EM=extensive metabolizers
ER=emergency room
FDA=Food and Drug Administration
$FEF_{25\%-75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity
FEV_1=forced expiratory volume in 1 second
FFS=fee for service
FRC=forced residual capacity
fu=unbound fraction
FVC=forced vital capacity
GI=gastrointestinal
GLS=geometric least squares
GOF=gain-of-function
GP=glycoprotein
GUSTO=Global Strategies for Opening Occluded Coronary Arteries
Hb=hemoglobin
HbA_{1c}= hemoglobin A_{1c}
HCUP=Healthcare Cost and Utilization Project
HF=heart failure
HFHS=Henry Ford Health System
HIRD^{SM}= HealthCore Integrated Research Database
HMG-Co A= 3-hydroxy-3-methyl-glutaryl-CoA
HPR=high platelet reactivity
HR=hazard ratio
HRQoL=health-related quality of life
HTN=hypertension
ICD-9=*International Classification of Diseases, 9th Edition/Revision*
ICER=incremental cost-effectiveness ratio
ICH=intracranial hemorrhage
ICU=intensive care unit
IHD=ischemic heart disease
IL-6=interleukin-6
INR=international normalized ratio
IPA=inhibition of platelet aggregation
IQR=interquartile range
IV=intravenous
K-M=Kaplan-Meier
LBBB=left bundle branch block
LD=loading dose
LLN=lower limit of normal
LMWH=low-molecular-weight heparin
LOF=loss-of-function
LOS=length of stay
LTA=light transmittance aggregometry
LVEF=left ventricular ejection fraction

MCO=managed care organization
MD=maintenance dose
MDRD=Modification of Diet in Renal Disease
MI=myocardial infarction
MPO=myeloperoxidase
MPR=medication possession ratio
NDDF=National Drug Data File
NDC=national drug code
NIS=nationwide inpatient sample
NNT=number needed to treat
NOS=not otherwise specified
NR=not reported
NS=not significant
NSAIDs=nonsteroidal anti-inflammatory drugs
NSTE=non–ST-segment elevation
NSTEMI=non–ST-segment elevation myocardial infarction
NSVT=nonsustained ventricular tachycardia
NT-proBNP=N-terminal pro-brain natriuretic peptide
OR=odds ratio
PBO=placebo
PCI=percutaneous coronary intervention
PCS=physical component summary
PD=pharmacodynamics
PEGASUS-TIMI 54=PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome
PES=paxlitaxel-eluting stent
PFTs=pulmonary function tests
PK=pharmacokinetics
PLATO=PLATelet inhibition and patient Outcomes
PLT=platelets
PPI=proton pump inhibitor
PPO=preferred provider organization
PRBCs=packed red blood cells
PRI=platelet reactivity index
PRU=$P2Y_{12}$ reaction units
Pts=patients
PTCA=percutaneous transluminal coronary angioplasty
PTMPM=per treated member per month
QALY=quality-adjusted life year
QTcB=QT interval corrected for heart rate using the Bazett correction
QTcF=QT interval corrected for heart rate using the Fredericia correction
QTcX=QT interval corrected by using a study-specific factor
RBCs=red blood cells
RI=recurrent ischemia
ROW=rest of the world
RR=relative risk
RRR=relative risk reduction
RV=residual volume
S=second(s)
SA=sinoatrial node
SAEs=serious adverse events
sCD40L=soluble CD40 ligand
SCr=serum creatinine
SD=standard deviation
SE=standard error
SES=sirolimus-eluting stent
SF-36=Health Survey Short Form 36 Item
SG=serum glucose
SpO_2=blood oxygen saturation
SRI=severe recurrent ischemia
SSDI=Social Security Death Index
STE-ACS=ST elevation–acute coronary syndrome
STEMI=ST-segment elevation myocardial infarction
SVT=supraventricular tachycardia
$t_{½}$=terminal half-life
TCG=ticagrelor
TLC=total lung capacity
T_{max}=time required to reach maximum plasma concentration
TIA=transient ischemic attack
TIMI=Thrombolysis in Myocardial Infarction
TnI=troponin I
TnT=troponin T
TRITON-TIMI 38=Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel
TTP=thrombotic thrombocytopenic purpura
UA=unstable angina
UFH=unfractionated heparin
UK=United Kingdom
ULN=upper limit of normal
US=United States
VASP=vasodilator-stimulated phosphoprotein
VN=VerifyNow
VT=ventricular tachycardia
WAC=wholesale acquisition cost
Wt=wild type

SECTION 1.0 Executive Summary

1.0 Executive Summary

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (unstable angina [UA], non ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) (BRILINTA Prescribing Information). BRILINTA, as compared to clopidogrel, reduced the rate of the combined endpoint of CV death, myocardial infarction (MI), or stroke in patients with ACS by 16% (relative risk reduction [RRR], p<0.001); absolute risk reduction [ARR] 1.9%.) The difference between treatments was driven by CV death and MI, with no difference in stroke. In patients treated with percutaneous coronary intervention (PCI), it also reduces the rate of definite stent thrombosis. Maintenance doses of aspirin (ASA) above 100 mg reduce the effectiveness of BRILINTA and should be avoided. The overall rate of PLATO-defined total major bleeding was similar between the BRILINTA and clopidogrel groups. BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. Please see the full Prescribing Information, including boxed warnings, for BRILINTA.

Boxed Warnings

Warning: Bleeding Risk

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding.
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage.
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery.
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of BRILINTA.
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent CV events.

Warning: Aspirin Dose and Brilinta Effectiveness

- Maintenance doses of ASA above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with ASA 75-100 mg per day.

1.1 Clinical Benefits

The efficacy and safety of ticagrelor was evaluated in the PLATO trial, a multinational, randomized, double-blind, double dummy, event-driven study that compared ticagrelor to clopidogrel for the reduction of CV events in 18,624 patients with UA, NSTEMI, or STEMI. Patients were randomized within 24 hours of their ACS event to either ticagrelor (180 mg loading dose [LD] followed by 90 mg twice daily) or clopidogrel (300 mg LD followed by 75 mg once daily). Patients in the ticagrelor arm who were undergoing PCI over 24 hours after randomization received an additional LD of ticagrelor 90 mg. Patients in the clopidogrel arm who were undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization. In addition to standard therapy, all patients received a daily maintenance ASA dose (75-100 mg was recommended, but higher maintenance doses of ASA were allowed according to local judgment), unless intolerant. Patients could be medically or invasively managed, with PCI or CABG, and were treated for 6 to 12 months. At 12 months, patients who received ticagrelor had a 16% RRR in the composite primary endpoint (rate of CV death, MI, or stroke) compared to those receiving clopidogrel (p<0.001; 1.9% ARR; number needed to treat [NNT]=54) (Wallentin et al, 2009a; Wallentin et al, 2009c Oral Presentation). Treatment with ticagrelor resulted in a 21% RRR in CV death and a 16% RRR in MI alone compared to clopidogrel (p=0.0013 and 0.0045, respectively). There was a nominally significant reduction in the rate of all-cause death with ticagrelor vs clopidogrel (4.5% vs. 5.9%, respectively). Definite stent thrombosis (an exploratory endpoint) was lower among ticagrelor treated patients compared to clopidogrel-treated patients (1.3% vs 1.9%, respectively) (Wallentin et al, 2009a).

The occurrence of the primary safety endpoint, PLATO-defined total major bleeding, was similar between the 2 treatment groups (11.6% and 11.2% for the ticagrelor- and clopidogrel-treated groups, respectively; p=0.43). There was no difference between treatment groups in the overall rate of fatal bleeding (0.3% for both groups; p=0.66). Within the fatal bleeding category, the rate of fatal nonintracranial bleeding was greater in the clopidogrel group (n=21 [0.3%] than the ticagrelor group (n=9 [0.1%]); p=0.03) while a greater number of fatal intracranial bleeds occurred in the ticagrelor group (n=11 [0.1%]) vs. the clopidogrel group (n=1 [0.01%]); p=0.02). Ticagrelor was associated with a higher rate of PLATO-defined non-CABG major bleeding than clopidogrel (4.5% vs. 3.8%, respectively; p=0.03). Dyspnea was reported in 13.8% of ticagrelor- and 7.8% of clopidogrel-treated patients, with 0.9% and 0.1% of patients, respectively, discontinuing study treatment as a result (p<0.001 for both comparisons). In the first week, ventricular pauses lasting >3 seconds occurred in 5.8% and 3.6% of patients receiving ticagrelor and clopidogrel, respectively (p=0.01). By Day 30, the incidence of ventricular pauses lasting >3 seconds was 2.1%

in patients receiving ticagrelor and 1.7% in patients receiving clopidogrel (p=0.52). There were no statistical differences in the occurrence of bradycardia, pacemaker insertion, syncope, or heart block between groups. Pauses were rarely associated with symptoms. (Wallentin et al, 2009a).

Higher doses of aspirin do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA. Overall results of the PLATO trial favored BRILINTA when used with low maintenance doses (≤ 100 mg) of ASA, and results analyzed by ASA dose were similar in the US and elsewhere (BRILINTA Prescribing Information). After PCI it is reasonable to use 81 mg of ASA per day in preference to higher maintenance doses (Levin et al, 2011).

Distinguishing characteristics of BRILINTA:

- Efficacy versus Clopidogrel: BRILINTA as compared to clopidogrel has been shown to decrease the rate of the combined endpoint of CV death, MI, or stroke in patients with ACS (16% RRR; 1.9% ARR). BRILINTA also significantly reduced the rate of CV death versus clopidogrel (21% RRR; 1.1% ARR). (Wallentin et al, 2006a).
- Stent Thrombosis: Among 11,289 patients with PCI receiving any stent during PLATO, there was a lower risk of definite stent thrombosis for ticagrelor (1.3%) than with clopidogrel (1.9%). The results were similar for drug-eluting and bare metal stents (BRILINTA Prescribing Information).
- Chemical Class: Ticagrelor is a member of the chemical class cyclo-pentyl-triazolo-pyrimidine (CPTP), which is a selective adenosine diphosphate (ADP) -receptor antagonist. Ticagrelor reversibly interacts with the platelet $P2Y_{12}$ ADP receptor to prevent signal transduction and platelet activation (BRILINTA Prescribing Information)
- Pharmacogenetics: There are no known genetic subtypes that impact the efficacy or safety of ticagrelor, including cytochrome (CYP) 2C19 (BRILINTA Prescribing Information).
- Use with Other Concomitant Therapy: BRILINTA can be administered with unfractionated or low molecular weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (BRILINTA Prescribing Information).
- Direct Acting: Ticagrelor is orally active; it does not require metabolic activation to exert its pharmacologic action. CYP3A is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite, AR C124910XX. The systemic exposure of the active metabolite is approximately 30-40% of the exposure of ticagrelor (Husted et al, 2006; BRILINTA Prescribing Information).
- Rapid Inhibition of Platelet Aggregation (IPA): Gurbel et al evaluated the onset of IPA of ticagrelor 180 mg versus clopidogrel 600 mg in patients with stable coronary artery disease, receiving background therapy with aspirin. On day 1, the IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours (Gurbel et al, 2009; BRILINTA Prescribing Information). It is not known how either bleeding risk or thrombotic risk correlate with IPA, for either ticagrelor or clopidogrel.

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage, active bleeding, or severe hepatic impairment. BRILINTA is metabolized by CYP 450, specifically CYP3A4/5. Avoid use with potent CYP3A inhibitors and strong CYP3A inducers. Avoid simvastatin and lovastatin doses greater than 40 mg. Monitor digoxin levels with the initiation of, or any change in BRILINTA therapy (BRILINTA Prescribing Information).

1.2 Economic Benefits

The unit cost of ticagrelor is provided in the table below (BRILINTA Prescribing Information)

Brand	Description	Package Size	NDC	WAC[a]	
BRILINTA® (ticagrelor)	Round, biconvex, yellow, film-coated tablet marked with "90" above "I" on one side	Bottles of 60 100 count hospital unit dose	0186-0777-60 0186-0777-39	Per Tablet $3.84	Per Day $7.68

NDC = National Drug Code; WAC = Wholesale Acquisition Cost
[a] Prices effective as of 1/6/2012.

A health economic substudy of the PLATO trial evaluated resource use patterns (as measured by all-cause inpatient bed days, investigations [eg, electocardiograms], CV interventions [eg, revascularization procedures], and bleeding

related utilization [eg, red blood cell products]) across different countries and regions to estimate US-specific costs (In House Data). Resource use data were collected on all patients within PLATO with a majority of the patients (82.9%) being discharged from hospital on low-dose ASA (≤100 mg/day) in addition to either clopidogrel or ticagrelor. The US costs were obtained from a single academic institution and may not be generalizable to other institutions. The study focused on medical care cost offset, and excluded medication costs.

The study demonstrated that ticagrelor use was associated with fewer resource utilization and medical care cost-offset compared with clopidogrel. In patients eligible for 12-month follow-up (n=10,686), ticagrelor use resulted in an estimated reduction in cumulative medical care costs of $1019 (95% CI: -101 to 2138) per patient over clopidogrel. Of the total estimated medical care cost reduction, an estimated $821 (80.6%) per patient cost offset was realized with ticagrelor compared with clopidogrel during the follow-up period after index hospitalization in patients eligible for 12 months of follow-up. The medical care cost offset with ticagrelor over clopidogrel was primarily driven by fewer all-cause inpatient bed days and CV interventional procedures (eg, PCIs and CABGs) per patient with ticagrelor as compared with clopidogrel (In House Data).

1.3 Conclusion

BRILINTA as compared to clopidogrel has been shown to decrease the rate of the combined endpoint of CV death, MI, or stroke in patients with ACS (16% RRR; 1.9% ARR). The difference between treatments was driven by CV death and MI, with no difference in stroke. BRILINTA significantly reduced the rate of CV death versus clopidogrel (21% RRR; 1.1% ARR). Treatment with ticagrelor also resulted in a 16% RRR in MI alone compared to clopidogrel (0.0045). Among 11,289 patients with PCI receiving any stent during PLATO, there was a lower risk of definite stent thrombosis for ticagrelor (1.3%) than with clopidogrel (1.9%). The overall rate of PLATO-defined total major bleeding was similar between the BRILINTA and clopidogrel groups. BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel.

Please see the full Prescribing Information, including boxed warnings, for BRILINTA.

Reference(s):

- BRILINTA Prescribing Information.
- Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation*. 2009;120:2577-2585.
- Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006;27:1038-1047.
- In House Data. Study of Platelet Inhibition and Patient Outcomes (PLATO) health economics (HECON) substudy. AstraZeneca LP, 2011.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [published online ahead of print November 7, 2011]. *J Am Coll Cardiol*. 2011;58(24). Available at: http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.08.007v1.pdf Accessed February 26, 2012..
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009a;361:1045-1057.
- Wallentin L, Becker RC, Budaj A, et al. for the PLATO investigators. Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results of the PLATelet inhibition and patient Outcomes (PLATO) trial [oral presentation]. *Eur Heart J*. 2009;30:1039-1108. Abstract 179-180.

SECTION 2.0 Product Information and Disease Description

2.1 PRODUCT DESCRIPTION

2.1.1 PRODUCT NAME

BRILINTA® (ticagrelor) tablets. BRILINTA is classified as an oral antiplatelet agent.

2.1.2 DOSAGE FORMS, NATIONAL DRUG CODES, AND WHOLESALE ACQUISITION COST

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on 1 side (BRILINTA Prescribing Information).

TABLE 2-1: BRILINTA Dosage Forms, Package Size, NDC, and WAC (BRILINTA Prescribing Information).[a]

Strength	Package Size	NDC #	WAC	
			Per Tablet	Per Day
Ticagrelor 90 mg tablets	Bottles of 60	0186-0777-60	$3.84	$7.68
Ticagrelor 90 mg tablets	100 count Hospital Unit Dose	0186-0777-39	$3.84	$7.68

NDC = national drug codes; WAC = wholesale acquisition cost. [a] Prices effective as of 1/6/12.

2.1.3 AHFS DRUG CLASSIFICATION

Platelet-Aggregation Inhibitor 20:12:18

2.1.4 FDA APPROVED INDICATION(S) AND OTHER STUDIED INDICATIONS

FDA Approved Uses (Date of approval: July 20, 2011)

Acute Coronary Syndromes (UA, NSTEMI, or STEMI)

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic CV events in patients with ACS (US, NSTEMI, or STEMI). BRILINTA has been shown to reduce the rate of a combined endpoint of CV death, MI or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with ASA. Maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of ASA above 100 mg daily.

2.1.5 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily.

After the initial loading dose of aspirin (ASA) (usually 325 mg), use BRILINTA with a daily maintenance dose of ASA of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

2.1.6 PHARMACOLOGY

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

2.1.7 PHARMACODYNAMICS/PHARMACOKINETICS

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2-1, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP.

As shown in Figure 2-2, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 2-2 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

FIGURE 2-1: Mean Inhibition of Platelet Aggregation (±SE) Following Single Oral Doses of Placebo, 180 mg Ticagrelor, or 600 mg Clopidogrel (BRILINTA Prescribing Information).

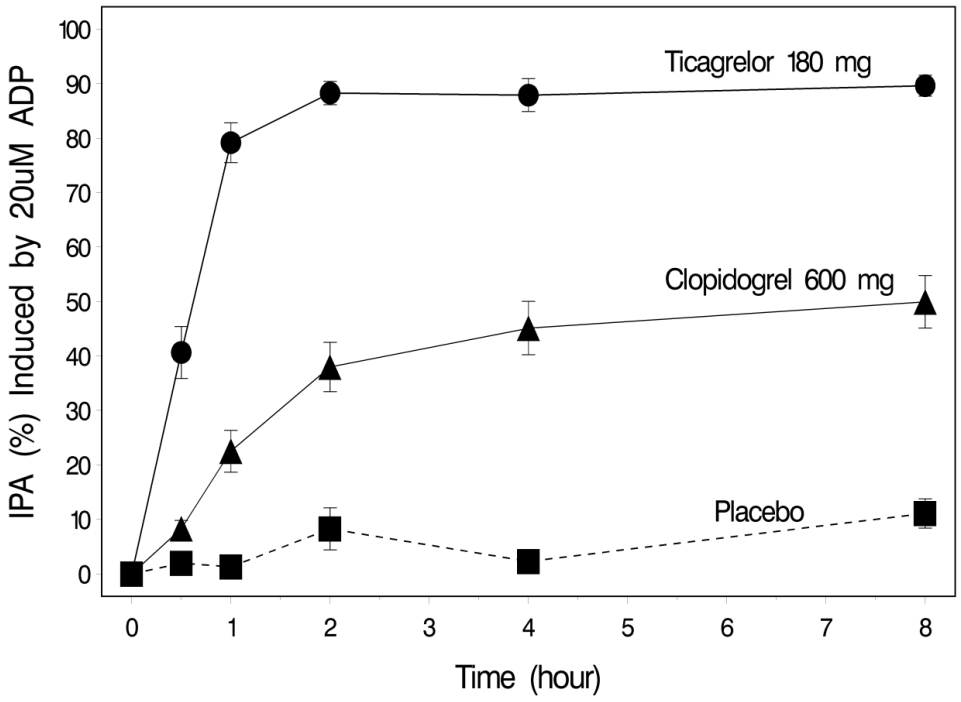
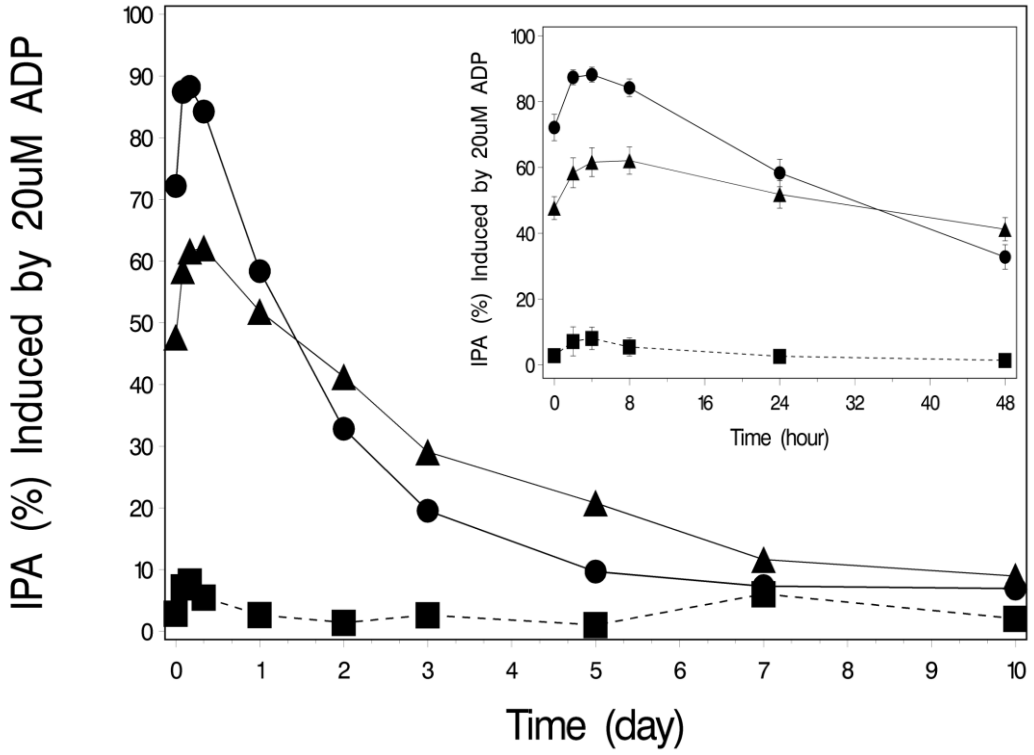


FIGURE 2-2: Mean Inhibition of Platelet Aggregation (IPA) Following 6 Weeks on Placebo, Ticagrelor 90 mg Twice Daily, or Clopidogrel 75 mg Daily (BRILINTA Prescribing Information).



circles=ticagrelor; triangles=clopidogrel; squares=placebo.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect.

2.1.8 CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The use of BRILINTA is contraindicated in the following conditions (BRILINTA Prescribing Information):

- History of Intracranial Hemorrhage. BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.
- Active Bleeding. BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- Severe Hepatic Impairment. BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins

Please refer to the full Prescribing Information for further details related to contraindications.

Warnings and Precautions

<u>General Risk of Bleeding</u>

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased.

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (eg, anticoagulant and fibrinolytic therapy, higher doses of ASA, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA 5 days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events.

Concomitant ASA Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of ASA (usually 325 mg), use BRILINTA with a maintenance dose of ASA of 75-100 mg.

Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after 1 month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (eg, to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of MI, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.

Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital.

2.1.9 DRUG INTERACTIONS

Please refer to the Product Comparison Table in Section 2.1.12 of this dossier for information related to drug interactions.

2.1.10 ADVERSE REACTIONS

Please refer to the full Prescribing Information for more detailed discussion related to adverse reactions (BRILINTA Prescribing Information).

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

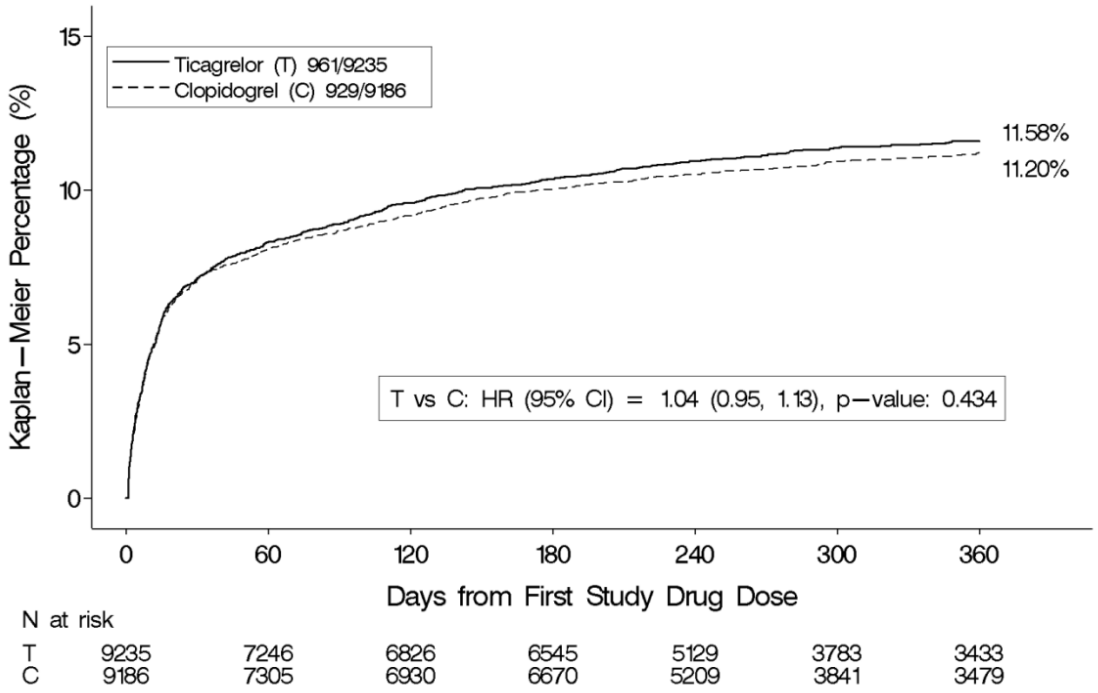
Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (eg, intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (eg, bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment.

The following figure shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

FIGURE 2-3 - Kaplan-Meier Estimate of Time to First PLATO-defined 'Total Major' Bleeding Event



Annualized rates of bleeding are summarized in the table below. About half of the bleeding events were in the first 30 days.

TABLE 2-2: Non-CABG-related Bleeds (KM%).

	BRILINTA n=9235	**Clopidogrel n=9186**
Total (major + minor)	8.7	7.0
Major	4.5	3.8
Fatal/life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/life-threatening	0.3	0.2

As shown in the preceding table, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in the following table. Rates were very high but similar for BRILINTA and clopidogrel.

TABLE 2-3: CABG Bleeds (KM%).

	Patients with CABG	
	BRILINTA n=770	**Clopidogrel n=814**
Total major	85.8	86.9
Fatal/life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in in vitro tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA-treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of nonhemorrhagic adverse events (AEs) occurred in PLATO at rates of 3% or more. These are shown in the following table. In the absence of a placebo control, whether these are drug-related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

TABLE 2-4: Percentage of Patients Reporting Non-hemorrhagic AEs at Least 3% or More in Either Group.

	BRILINTA n=9235	**Clopidogrel n=9186**
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a] Includes dyspnea, dyspnea extertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal.

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (eg, patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope, and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the 2 treatment groups in PLATO.

Lab Abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious AEs such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

2.1.11 ACCESS (EG, RESTRICTIONS ON DISTRIBUTION, SUPPLY LIMITATIONS, ANTICIPATED SHORTAGES, AND/OR PRESCRIBING RESTRICTIONS)

WARNING: ASA Dose and BRILINTA Effectiveness

Maintenance doses of ASA above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with ASA 75-100 mg per day.

2.1.12 CO-PRESCRIBED/CONCOMITANT THERAPIES

Multiple concurrent pharmacologic treatments are required for ACS (Anderson et al, 2007). For UA/NSTEMI, treatment with major drug classes includes anti-ischemic therapy, antiplatelet agents, and anticoagulant treatment. Besides supplemental oxygen, anti-ischemic drugs include nitroglycerin, oral beta-blockers within the first 24 hours if not contraindicated, and angiotensin-converting enzyme inhibitors (ACE-Is) for patients with pulmonary congestion or left ventricular ejection fraction ≤40%. Antiplatelet therapy is comprised of ASA, clopidogrel, and GP IIb/IIIa inhibitors. Anticoagulant therapy includes unfractionated heparin, fondaparinux, enoxaparin, and bilvalrudin.

2.1.12 PRODUCT COMPARISON TABLE

The information presented in the following table has been derived exclusively from the respective Prescribing Information. Additional information may be available in the published literature but was not included in the table unless otherwise noted.

TABLE 2-3: Oral Antiplatelet Agents.

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Indication(s)			
ACS BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic CV events in patients with ACS (US, NSTEMI, or STEMI). BRILINTA has been shown to reduce the rate of a combined endpoint of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. BRILINTA has been studied in ACS in combination with ASA. Maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of ASA above 100 mg daily.	ACS For patients with non-ST-segment elevation ACS (UA/NSTEMI) including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of CV death, MI, or stroke as well as the rate of a combined endpoint of CV death, MI, stroke, or refractory ischemia. For patients with STEMI, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. The optimal duration of Plavix therapy in ACS is unknown. Recent MI, Recent Stroke, or Established Peripheral Arterial Disease For patients with a history of recent MI, recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.	ACS Effient is indicated to reduce the rate of thrombotic CV events (including stent thrombosis) in patients with ACS who are to be managed with PCI as follows: • Patients with UA or NSTEMI • Patients with STEMI when managed with primary or delayed PCI Effient has been shown to reduce the rate of a combined endpoint of CV death, nonfatal MI, or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death. It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many CV events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.	Indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors or who have had a completed thrombotic stroke. Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including TTP, neutropenia/agranulocytosis, and aplastic anemia, ticlopidine should be reserved for patients who are intolerant or allergic to ASA therapy or who have failed ASA therapy. As adjunctive therapy with ASA to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation.

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Boxed Warning			
WARNING: BLEEDING RISK • BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding. • Do not use BRILINTA in patients with active pathological bleeding or a history of ICH. • Do not start BRILINTA in patients planned to undergo urgent CABG. When possible, discontinue BRILINTA at least 5 days prior to any surgery. • Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of BRILINTA. • If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent CV events. **WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS** • Maintenance doses of ASA above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with ASA 75-100 mg per day.	**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS** The effectiveness of Plavix is dependent on its activation to an active metabolite by the CYP system, principally CYP2C19. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with ACS or undergoing PCI treated with Plavix at recommended doses exhibit higher CV event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.	**WARNING: BLEEDING RISK** Effient can cause significant, sometimes fatal, bleeding. Do not use Effient in patients with active pathological bleeding or a history of TIA or stroke. In patients ≥75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered. Do not start Effient in patients likely to undergo urgent CABG surgery. When possible, discontinue Effient at least 7 days prior to any surgery. Additional risk factors for bleeding include: • Body weight <60 kg • Propensity to bleed • Concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, chronic use of NSAIDS) Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of Effient. If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after ACS, increases the risk of subsequent CV events.	**WARNING:** Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, TTP, and aplastic anemia. <u>Neutropenia/Agranulocytosis</u> Among 2048 patients in clinical trials in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of those patients (0.8% of the total population). <u>TTP</u> One case of TTP was reported during clinical trials in stroke patients. Based on postmarketing data, US physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as 1 case in every 2000 to 4000 patients exposed.

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Dosing			
Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) LD and continue treatment with 90 mg twice daily. After the initial LD of ASA (usually 325 mg), use BRILINTA with a daily maintenance dose of ASA of 75-100 mg. ACS patients who have received a LD of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.	ACS Plavix can be administered with or without food. • For patients with UA/NSTEMI ACS, initiate Plavix with a single 300 mg oral LD and then continue at 75 mg QD. Initiate ASA (75–325 mg QD) and continue in combination with Plavix. • For patients with STEMI, the recommended dose of Plavix is 75 mg QD orally, administered in combination with ASA (75–325 mg QD), with or without thrombolytics. Plavix may be initiated with or without a LD. Recent MI, Recent Stroke, or Established Peripheral Arterial Disease The recommended daily dose of Plavix is 75 mg QD orally, with or without food. CYP2C19 Poor Metabolizers CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established. Use with PPIs Avoid using omeprazole or esomeprazole with Plavix. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of Plavix. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.	ACS Initiate Effient treatment as a single 60 mg oral LD and then continue at 10 mg orally QD. Patients taking Effient should also take ASA (75 mg to 325 mg) daily. Effient may be administered with or without food. Dosing in Low Weight Patients Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg QD maintenance dose. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.	Stroke The recommended dose of ticlopidine is 250 mg BID taken with food. Coronary Artery Stenting The recommended dose of ticlopidine is 250 mg BID taken with food together with antiplatelet doses of ASA for up to 30 days of therapy following successful stent implantation.
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Mechanism of action			
Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.	Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.	Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.	Interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect on platelet function is irreversible for the life of the platelet.

Ticagrelor[a] (BRILINTA®)

Adverse Reactions

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in Hb of more than 5 g/dL; transfusion of 4 or more units (whole blood or PRBCs) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (eg, intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (eg, bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Annualized rates of bleeding are summarized below. About half of thebleeding events were in the first 30 days.

Non-CABG-related bleeds (KM%)

	BRILINTA n=9235	**Clopidogrel n=9186**
Total (major + minor)	8.7	7.0
Major	4.5	3.8
Fatal/life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/life-threatening	0.3	0.2

BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown below. Rates were very high but similar for BRILINTA and clopidogrel.

CABG Bleeds (KM%).

	Patients with CABG	
	BRILINTA n=770	**Clopidogrel n=814**
Total major	85.8	86.9
Fatal/life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in in vitro tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common AEs

A variety of nonhemorrhagic AEs occurred in PLATO at rates of 3% or more. These are shown in the table below. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Percentage of Patients Reporting Nonhemorrhagic AEs at Least 3% or More in Either Group.

	BRILINTA n=9235	**Clopidogrel n=9186**
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a]Includes dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal.

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (eg, patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid: Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related SAEs such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

Clopidogrel[b] (Plavix®)

Adverse Reactions

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Bleeding
- TTP

Bleeding

CURE

In CURE, Plavix use with ASA was associated with an increase in major bleeding (primarily GI and at puncture sites) compared to placebo with ASA. The incidence of ICH (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

Overall Incidence of Bleeding in CURE (% Patients)

Event	Plavix (+ASA)[a]	Placebo (+ASA)[a]
Major Bleeding[b]	**3.7[c]**	**2.7[d]**
Life-threatening bleeding	2.2	1.8
Fatal	0.2	0.2
5 g/dL Hb drop	0.9	0.9
Required surgical intervention	0.7	0.7
Hemorrhagic strokes	0.1	0.1
Required inotropes	0.5	0.5
Required transfusion (≥4 units)	1.2	1.0
Other Major Bleeding	**1.6**	**1.0**
Significantly disabling	0.4	0.3
Intraocular bleeding with significant loss of vision	0.05	0.03
Required 2-3 units of blood	1.3	0.9
Minor Bleeding[e]	**5.1**	**2.4**

[a]Other standard therapies were used as appropriate; [b]Life-threatening and other major bleeding; [c]Major bleeding event rate for Plavix+ASA was dose-dependent on ASA: <100 mg = 2.6%; 100–200 mg = 3.5%; >200 mg = 4.9%; Major bleeding event rates for Plavix+ASA by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years = 5.9%; [d]Major bleeding event rate for placebo+ASA was dose-dependent on ASA: <100 mg = 2.0%; 100–200 mg = 2.3%; >200 mg = 4.0%; Major bleeding event rates for placebo+ASA by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%; [e]Led to interruption of study medication

92% of the patients in the CURE study received heparin or LMWH, and the rate of bleeding in these patients was similar to the overall results.

COMMIT

In COMMIT, similar rates of major bleeding were observed in the Plavix and placebo groups, both of which also received ASA.

Incidence of Bleeding Events in COMMIT (% Patients)

Type of bleeding	Plavix (+ ASA) n=22,961	Placebo (+ASA) n=22,891	p-value
Major[a] noncerebral or cerebral bleeding[b]	**0.6**	**0.5**	**0.59**
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	**0.2**	**0.2**	**0.91**
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (nonmajor)	**3.6**	**3.1**	**0.005**
Any noncerebral bleeding	**3.9**	**3.4**	**0.004**

[a]Major bleeds were cerebral bleeds or noncerebral bleeds thought to have caused death or that required transfusion; [b]The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Plavix+ASA by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years = 0.8%. Event rates for placebo+ASA by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years = 0.7%.

CAPRIE (Plavix vs. ASA)
In CAPRIE, GI hemorrhage occurred at a rate of 2.0% in those taking Plavix vs. 2.7% in those taking ASA; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of ICH was 0.4% for Plavix compared to 0.5% for ASA.

Other bleeding events that were reported more frequently in the Plavix group were epistaxis and hematoma.

Other AEs
In CURE and CHARISMA, which compared Plavix plus ASA to ASA alone, there was no difference in the rate of AEs (other than bleeding) between Plavix and placebo.

In CAPRIE, which compared Plavix to ASA, pruritus was more frequently reported in those taking Plavix. No other difference in the rate of AEs (other than bleeding) was reported.

Prasugrel[c] (Effient®)

Adverse Reactions

The following serious adverse reactions are also discussed elsewhere in the labeling:

- Bleeding
- TTP

Safety in patients with ACS undergoing PCI was evaluated in a clopidogrel-controlled study, TRITON-TIMI 38, in which 6741 patients were treated with Effient (60 mg LD and 10 mg once daily) for a median of 14.5 months (5802 patients were treated for over 6 months; 4136 patients were treated for more than 1 year). The population treated with Effient was 27 to 96 years of age, 25% female, and 92% Caucasian. All patients in the TRITON-TIMI 38 study were to receive ASA. The dose of clopidogrel in this study was a 300 mg LD and 75 mg once daily.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared with the rates observed in other clinical trials of another drug and may not reflect the rates observed in practice.

Drug Discontinuation
The rate of study drug discontinuation because of adverse reactions was 7.2% for Effient and 6.3% for clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for Effient and 1.4% for clopidogrel).

Bleeding
Bleeding Unrelated to CABG Surgery – In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated CABG were significantly higher on Effient than on clopidogrel, as shown in the following table.

Non-CABG-Related Bleeding[a] (TRITON-TIMI 38)

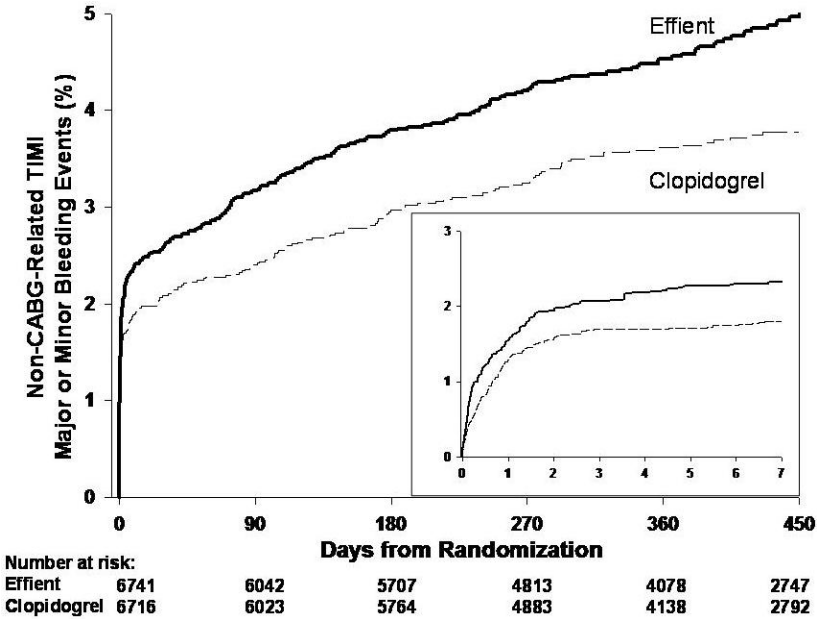
	Effient (%) n=6741	Clopidogrel (%) n=6716	p-value
TIMI Major or Minor bleeding	4.5	3.4	0.002
TIMI Major Bleeding[b]	2.2	1.7	0.029
Life-threatening	1.3	0.8	0.015
Fatal	0.3	0.1	—
Symptomatic ICH	0.3	0.3	—
Requiring inotropes	0.3	0.1	—
Requiring surgical intervention	0.3	0.3	—
Requiring transfus o (≥4 units)	0.7	0.5	—
TIMI Minor Bleeding[b]	2.4	1.9	0.022

[a]Patients may be counted in more than 1 row; [b]Major (clinically overt bleeding associated with a fall in Hb ≥5 g/dL, or ICH) and TIMI Minor (overt bleeding associated with a fall in Hb of ≥3 g/dL but <5 g/dL).

The following figure demonstrates non-CABG related TIMI Major or Minor bleeding. The bleeding rate is highest initially, as shown in the following figure (inset: Days 0 to 7).

Bleeding rates in patients with the risk factors of age ≥75 years and weight <60 kg are shown in the next table.

Non-CABG-related TIMI Major or Minor Bleeding



Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	**Clopidogrel (%)**	**Effient (%)**	**Clopidogrel (%)**
Weight <60 kg (N=308 Effient, N=356 Clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥60 kg (N=6373 Effient, N=6299 Clopidogrel)	4.2	3.3	0.3	0.1
Age <75 years ((N=5850 Effient, N=5822 Clopidogrel)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 Clopidogrel)	9.0	6.9	1.0	0.1

Bleeding Related to CABG

In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the course of the study. The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient group and 4.5% in the clopidogrel group. The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from the most recent dose of study drug.

CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) n=213	**Clopidogrel (%) n=224**
TIMI Major or Minor Bleeding	14.1	4.5
TIMI Major Bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion ≥5 units	6.6	2.2
ICH	0	0
TIMI Minor Bleeding	2.8	0.9

[a]Patients may be counted in more than 1 row.

Bleeding Reported as Adverse Reactions – Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), GI hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

Malignancies

During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences.

Other AEs

In TRITON-TIMI 38, common and other important nonhemorrhagic AEs were, for Effient and clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). The following table summarizes the AEs reported by at least 2.5% of patients.

Non-Hemorrhagic Treatment Emergent AEs Reported by at Least 2.5% of Patients in Either Group

	Effient (%) (n=6741)	**Clopidogrel (%) (n=6716)**
Hypertension	7.5	7.1
Hypercholesterolemia/ Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia ($<4 \times 10^9$ WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

Postmarketing Experience
The following adverse reactions have been identified during post approval use of Effient. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders — Thrombocytopenia, TTP

Immune system disorders — Hypersensitivity reactions including anaphylaxis

Ticlopidine[d]

Adverse Reactions

From controlled studies: TASS and CATS (n=2048)

Percentage of Patients With AEs in Controlled Studies (TASS and CATS)[a]

Event	Ticlopidine (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence
Any events	60.0 (20.9)	53.2 (14.5)	34.3 (6.1)
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0(1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritis	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal LFT	1.0 (0.7)	0.3 (0.3)	0.0(0.0)

[a]Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Hematological
Neutropenia/thrombocytopenia, TTP, aplastic anemia, leukemia, agranulocytosis, eosinophilia, pancytopenia, thrombocytosis, and bone-marrow depression have been reported.

GI
Ticlopidine therapy has been associated with a variety of GI complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1 to 2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. In some cases of severe or bloody diarrhea, colitis was later diagnosed.

Hemorrhagic
Ticlopidine has been associated with increased bleeding, spontaneous posttraumatic bleeding and perioperative bleeding including, but not limited to, GI bleeding. It has also been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, and conjunctival hemorrhage.

Intracerebral bleeding was rare in clinical trials in stroke patients with ticlopidine, with an incidence no greater than that seen with comparator agents (ticlopidine 0.5%, ASA 0.6%, placebo 0.75%). It has also been reported postmarketing.

Rash
Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes, including Stevens-Johnson syndrome, erythema multiforme, and exfoliative dermatitis.

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Contraindications			
History of ICH because of a high risk of recurrent ICH in this population Active pathological bleeding such as peptic ulcer or ICH Severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.	Active pathological bleeding such as peptic ulcer or ICH Hypersensitivity (eg, anaphylaxis) to clopidogrel or any component of the product	Active pathological bleeding such as peptic ulcer or ICH History of prior TIA or stroke. In TRITON-TIMI 38, patients with a history of TIA or ischemic stroke (>3 months prior to enrollment) had a higher rate of stroke on Effient (6.5%; of which 4.2% were thrombotic stroke and 2.3% were ICH than on clopidogrel (1.2%; all thrombotic). In patients without such a history, the incidence of stroke was 0.9% (0.2% ICH) and 1.0% (0.3% ICH) with Effient and clopidogrel, respectively. Patients with a history of ischemic stroke within 3 months of screening and patients with a history of hemorrhagic stroke at any time were excluded from TRITON-TIMI 38. Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued. Hypersensitivity (eg, anaphylaxis) to prasugel or any component of the product	Hypersensitivity to the drug Presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of either TTP or aplastic anemia Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding) Severe liver impairment
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Warnings and Precautions			
Please refer to the full **Boxed Warning** section above. General Risk of Bleeding Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (eg, anticoagulant and fibrinolytic therapy, higher doses of ASA, and chronic NSAIDs). When possible, discontinue BRILINTA 5 days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.	Please refer to the full **Boxed Warning** section above. Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function Clopidogrel is a prodrug. IPA by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. *Proton Pump Inhibitors* Avoid concomitant use of Plavix with omeprazole or esomeprozole because both significantly reduce the antiplatelet activity of Plavix. General Risk of Bleeding Thienopyridines, including Plavix, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Plavix 5 days prior to surgery. In patients who stopped therapy more than 5 days prior to CABG, the rates of major bleeding were similar (event rate 4.4% Plavix+ASA; 5.3% placebo+ASA). In patients who remained on therapy within 5 days of CABG, the major bleeding rate was 9.6% for Plavix+ASA, and 6.3% for	Please refer to the full **Boxed Warning** section above. General Risk of Bleeding Thienopyridines, including Effient, increase the risk of bleeding. With the dosing regimens used in TRITON-TIMI 38, TIMI Major (clinically overt bleeding associated with a fall in Hb ≥5 g/dL, orICH) and TIMI Minor (overt bleeding associated with a fall in Hb of ≥3 g/dL but <5 g/dL) bleeding events were more common on Effient than on clopidogrel. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures even if the patient does not have overt signs of bleeding. Do not use Effient in patients with active bleeding, prior TIA or stroke. Other risk factors for bleeding are: • Age ≥75 years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients ≥75 years of age, use of Effient is generally not recommended in these patients, except in high-risk situations	Please refer to the full **Boxed Warning** section above. Hematologic Adverse Reactions *Neutropenia* Neutropenia may occur suddenly. Bone-marrow examination typically shows a reduction in white blood cell precursors. After withdrawal of ticlopidine, the neutrophil count usually rises to >1200/mm^3 within 1 to 3 weeks. *Thrombocytopenia* Rarely, thrombocytopenia may occur in isolation or together with neutropenia *TTP* TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. *Aplastic Anemia* Aplastic anemia is characterized by anemia, thrombocytopenia, and neutropenia together with a bone marrow examination that shows decreases in

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent CV events.

Concomitant ASA Maintenance Dose
In PLATO, use of BRILINTA with maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial LD of ASA (usually 325 mg), use BRILINTA with a maintenance dose of ASA of 75-100 mg.

Moderate Hepatic Impairment
BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea
Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after 1 month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA
Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (eg, to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of MI, stent thrombosis, and death.

Strong Inhibitors of CYP3A
Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.

CYP3A Potent Inducers
Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital.

placebo+ASA.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7–10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the LD or 2 hours of the maintenance dose may be less effective.

Discontinuation of Plavix
Avoid lapses in therapy, and if Plavix must be temporarily discontinued, restart as soon as possible. Premature discontinuation of Plavix may increase the risk of CV events.

Patients with Recent TIA or Stroke
In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of ASA and Plavix has not been shown to be more effective than Plavix alone, but the combination has been shown to increase major bleeding.

TTP
TTP, sometimes fatal, has been reported following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

(patients with diabetes or history of MI) where its effect appears to be greater and its use may be considered.
- CABG or other surgical procedure
- Body weight <60 kg. Consider a lower (5 mg) maintenance dose.
- Propensity to bleed (eg, recent trauma, recent surgery, recent or recurrent GI bleeding, active peptic ulcer disease, or severe hepatic impairment).
- Medications that increase the risk of bleeding (eg, oral anticoagulants, chronic use of NSAIDs, and fibrinolytic agents). ASA and heparin were commonly used in TRITON-TIMI 38.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of prasugrel's active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 6 hours of the LD or 4 hours of the maintenance dose may be less effective.

CABG Surgery-Related Bleeding
The risk of bleeding is increased in patients receiving Effient who undergo CABG. If possible, Effient should be discontinued at least 7 days prior to CABG.

Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI Major or Minor bleeding were 14.1% in the Effient group and 4.5% in the clopidogrel group. The higher risk for bleeding events in patients treated with Effient persisted up to 7 days from the most recent dose of study drug. For patients receiving a thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12 of 45 patients) in the Effient group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.4% (3 of 89 patients) in the clopidogrel group.

Do not start Effient in patients likely to undergo urgent CABG. CABG-related bleeding may be treated with transfusion of blood products, including PRBCs and platelets; however, platelet transfusions within 6 hours of the LD or 4 hours of the maintenance dose may be less effective.

the precursor cells for RBCs, white blood cells, and platelets.

Other Hematological Effects
Rare cases of agranulocytosis, pancytopenia, or leukemia have been reported in postmarketing experience, some of which have been fatal. All forms of hematological adverse reactions are potentially fatal.

Cholesterol Elevation
Ticlopidine therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8% to 10% within 1 month of therapy and persist at that level.

Anticoagulant Drugs
The tolerance and long-term safety of coadministration of ticlopidine with heparin, oral anticoagulants, or fibrinolytic agents have not been established.

GI Bleeding
Ticlopidine prolongs template bleeding time. The drug should used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on ticlopidine.

Use in Hepatically Impaired Patients
Since ticlopidine is metabolized by the liver, dosing of ticlopidine or other drugs metabolized in the liver may require adjustment upon starting or stopping concomitant therapy. Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of ticlopidine is not recommended in this population.

		Discontinuation of Effient Discontinue thienopyridines, including Effient, for active bleeding, elective surgery, stroke, or TIA. The optimal duration of thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any antiplatelet medication, including thienopyridines, conveys an increased risk of stent thrombosis, MI, and death. Patients who require premature discontinuation of a thienopyridine will be at increased risk for cardiac events. Lapses in therapy should be avoided, and if thienopyridines must be temporarily discontinued because of an AE(s), they should be restarted as soon as possible. TTP TTP has been reported with the use of Effient. TTP can occur after a brief exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including plasmapheresis (plasma exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.	
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Half-life			
Approximately 7 hours for ticagrelor and 9 hours for its active metabolite	After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.	The active metabolite has an elimination half-life of about 7 hours (range: 2 to 15 hours).	Half-life of a single dose: approximately 12.6 hours Half-life after repeated doses: 4 to 5 days
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Time to Peak Plasma Concentration/Steady State			
Median t_{max} of 1.5 hours (range 1.0-4.0) for ticagrelor. Median t_{max} of 2.5 hours (range 1.5-5.0) for the formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor Steady state not available.	30 to 60 minutes after dosing; increasing the dose by a factor of 4 results in 2.0- and 2.7-fold increases in C_{max} and AUC, respectively. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7.	30 min/Mean steady-state IPA was about 70% following 3 to 5 days of dosing at 10 mg daily after a 60 mg LD of Effient.	Approximately 2 hours after dosing/ Steady state: approximately 14 to 21 days

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Absorption			
The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.	After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.	Following oral administration, ≥79% of the dose is absorbed.	Absorption is greater than 80%.
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Distribution			
The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).	Not available	Active metabolite: 44 to 68 L The active metabolite is bound about 98% to human serum albumin.	Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins. Approximately 40% to 50% of the radioactive metabolites circulating in plasma are covalently bound to plasma proteins.
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Metabolism			
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.	Extensively metabolized by 2 main metabolic pathways: 1 mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and 1 mediated by multiple CYP enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6, and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.	Rapidly hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19.	Ticlopidine hydrochloride is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine.

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Excretion			
The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion.	Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing.	Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites.	Following an oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity is recovered in the urine and 23% in the feces. Approximately 1/3 of the dose excreted in the feces is intact ticlopidine hydrochloride.
Ticagrelor[a] (BRILINTA®)	**Clopidogrel[b] (Plavix®)**	**Prasugrel[c] (Effient®)**	**Ticlopidine[d]**
Drug Interactions (Please consult the Prescribing Information for more detailed information regarding the nature and significance of these interactions.)			
Effects of Other Drugs Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5. CYP3A Inhibitors Avoid use of strong inhibitors of CYP3A (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin). CYP3A Inducers Avoid use with potent inducers of CYP3A (eg, rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital). ASA Use of BRILINTA with ASA maintenance doses above 100 mg reduced the effectiveness of BRILINTA. Effect of BRILINTA on Other Drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter. Simvastatin, Lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg. Digoxin Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy.	CYP2C19 Inhibitors Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. *PPIs* Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole. NSAIDs Coadministration of Plavix and NSAIDs increases the risk of GI bleeding. Warfarin (CYP2C9 Substrates) Although the administration of clopidogrel 75 mg per day did not modify the PK of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis. However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.	Warfarin Coadministration of Effient and warfarin increases the risk of bleeding. NSAIDs Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding. Other Concomitant Medications Effient can be administered with drugs that are inducers or inhibitors of CYP enzymes. Effient can be administered with ASA (75 mg to 325 mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including PPIs and H2 blockers. Potential for Other Drugs to Affect Prasugrel *Inhibitors of CYP3A* Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated IPA or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as verapamil, diltiazem, indinavir, ciprofloxacin, clarithromycin, and grapefruit juice are not expected to have a significant effect on the PK of the active metabolite of prasugrel. *Inducers of CYPs* Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the PK of prasugrel's active metabolite or its IPA. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of CYP are not expected to have significant effect on the PKs of the active metabolite of prasugrel.	• ASA and other NSAIDs: Ticlopidine potentiates the effect of ASA or other NSAIDs on platelet aggregation. • Cimetidine: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine by 50%. • Theophylline: In normal volunteers, concomitant administration of ticlopidine resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline.

Other Concomitant Therapy BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, PPIs, beta-blockers, angiotensin converting enzyme inhibitors, and ARBs.		*Drugs That Elevate Gastric pH* Daily coadministration of ranitidine (an H_2 blocker) or lansoprazole (a PPI) decreased the C_{max} of the prasugrel active metabolite by 14% and 29%, respectively, but did not change the active metabolite's AUC and T_{max}. In TRITON-TIMI 38, Effient was administered without regard to coadministration of a PPI or H_2 blocker. *Statins* Atorvastatin (80 mg daily), a drug metabolized by CYP3A4, did not alter the PK of prasugrel's active metabolite or its IPA. *Heparin* A single IV dose of UFH (100 U/kg) did not significantly alter coagulation or the prasugrel-mediated IPA; however, bleeding time was increased compared with either drug alone. *ASA* ASA 150 mg daily did not alter prasugrel-mediated IPA; however, bleeding time was increased compared with either drug alone. *Warfarin* A significant prolongation of the bleeding time was observed when prasugrel was coadministered with 15 mg of warfarin. Potential for Prasugrel to Affect Other Drugs In vitro metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A. *Drugs Metabolized by CYP2B6* Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%, an amount not considered clinically significant. Prasugrel is not anticipated to have significant effect on the PK of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine. *Effect on Digoxin* The potential role of prasugrel as a Pgp substrate was not evaluated. Prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration.	

Ticagrelor[a] (BRILINTA®)	Clopidogrel[b] (Plavix®)	Prasugrel[c] (Effient®)	Ticlopidine[d]
Pharmacogenomics			
In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.	• CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite PK and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite. • The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess 2 loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype. • A crossover study in 40 healthy subjects, 10 each in the 4 CYP2C19 metabolizer groups, evaluated PK and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished IPA were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see the following table). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.	There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the PK of prasugrel's active metabolite or its IPA.	No information

Active Metabolite PK and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose mg	UR	EX	IM	P
C_{max} ng/mL	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
IPA[a] %	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	60 (18)
	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)
VASP PRI[b] %	300 mg (24 h)	73 (12)	68 (16)	77 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)

Values are mean (SD); [a]IPA with 5 mcM ADP; larger value indicates greater platelet inhibition; [b]Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition.

- Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.
- The relationship between CYP2C19 genotype and Plavix treatment outcome was evaluated in retrospective analyses of Plavix-treated subjects in CHARISMA (n=4862) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of CV events (death, MI, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and 1 cohort study, the increased event rate was observed only in poor metabolizers.

Abbreviations: AEs = adverse events; ASA = aspirin; ACS = acute coronary syndrome; ARBs = angiotensin receptor blockers; CABG = coronary artery bypass graft; CV = cardiovascular; CYP = cytochrome P450; EX = extensive;GI = gastrointestinal; Hb = hemoglobin; ICH = intracranial hemorrhage; IM = intermediate; IPA = inhibition of platelet aggregation; LD = loading dose; LMWH = low molecular weight heparin; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; NSTEMI = non-ST-elevation myocardial infarction; P = poor; PCI = percutaneous coronary intervention; PK = pharmacokinetics; PPI = proton pump inhibitors; PRBCs = packed red blood cells; RBCs = red blood cells; SAEs = serious adverse events; STEMI = ST-elevation myocardial infarction, TIA = transient ischemic attack; TRITON-TIMI 38 = TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel; TTP = thrombotic thrombocytopenic purpura; UA = unstable angina; UR = ultrarapid; VASP-PRI = vasodilator-stimulated phosphoprotein–platelet reactivity index.

[a]BRILINTA Prescribing Information, July 2011. [b]Plavix (clopidogrel bisulfate) Prescribing Information, December 2011. [c]Effient (prasugrel) Prescribing Information, December 2010. [d]ticlopidine hydrochloride Prescribing Information, June 2003.

2.2 PLACE IN THERAPY

2.2.1 DISEASE DESCRIPTION

2.2.1.1 Epidemiology

The spectrum of clinical presentations ranging from UA through NSTEMI and STEMI is referred to as ACS. Patients with ACS present with symptoms resulting from myocardial ischemia. The pathophysiology of all 3 types of ACS originates with progression, instability, or rupture of a coronary plaque, with or without luminal thrombosis and vasospasm (Roger et al, 2011).

Major risk factors for CHD and subsequent ACS include smoking, family history, adverse lipid profiles, diabetes mellitus, and hypertension, each of which was identified in large epidemiologic studies conducted over long periods of time (Anderson et al, 2007).

The average age of men at the time of the first MI is 64.5 years. For women, the mean age at the time of the first MI is 70.3 years (Roger et al, 2012).

In 2009, the number of hospital discharges with ACS was estimated to be 683,000; the estimate was based on the sum of the first-listed inpatient hospital discharges for MI and those for UA. When secondary discharge diagnoses were included, the estimated number of unique hospitalizations for ACS was 1,190,000. Of this total, a diagnosis of MI accounted for 829,000 hospitalizations, a diagnosis of UA accounted for 357,000, and both diagnoses accounted for 4000 (Roger et al, 2012).

The estimated percentage of STEMI in the United States varies among registries and databases (Roger et al, 2012). STEMI occurs in approximately 29% of patients with MI, according to the National Registry of Myocardial Infarction 4. Similarly, the estimated percentage of patients with STEMI as determined by the AHA's Get With the Guidelines project is 32%. In addition, the Global Registry of Acute Coronary Events, in which the US patient population is included, has reported that STEMI occurs in approximately 38% of patients with ACS.

2.2.1.2 Pathophysiology

ACS is an acute event manifesting primarily as a result of longstanding atherosclerosis (Kumar and Cannon, 2009). Atherosclerosis is characterized by the accumulation of lipids and fibrous elements in arteries, which results in the formation of plaques. A ruptured or eroded atherosclerotic plaque within a coronary artery stimulates the process of thrombosis with platelet deposition severe enough to impede coronary flow and induce myocardial ischemia leading to ACS (Davies, 2000).

Platelet adherence to the subendothelium and collagen exposed by atherosclerotic plaque rupture results in platelet activation and the release or local accumulation of soluble platelet agonists (thrombin, ADP, and thromboxane A_2). ADP is vital for platelet aggregation and thrombus growth since, after secretion from the platelet, it amplifies the platelet response to other agonists by stimulating the $P2Y_{12}$ and $P2Y_1$ receptors on the platelets. Platelet aggregation, mediated by interaction between the activated platelet GP IIb/IIIa receptor and its ligands, results in the formation of a platelet-rich thrombus. This in turn causes further platelet aggregation, potentially further microembolization, coronary artery vasoconstriction, and subsequent reduction in coronary artery blood flow (Davies, 2000; Steinbuhl and Moliterno, 2005).

2.2.1.3 Clinical Presentation

ACS is a life-threatening atherothrombotic disease. To assist the health care provider in making decisions regarding medical management and coronary revascularization for a particular patient, criteria for risk stratification have been developed. Although the main symptom that initiates the diagnostic and therapeutic cascade is chest pain, the classification of ACS is based on ECG results (Bassand et al, 2007).

UA and NSTEMI are conditions whose pathogenesis and clinical presentation are similar but whose severity differs; that is, these conditions differ mainly in whether the ischemia is of sufficient severity to induce myocardial damage and the subsequent release of biomarkers of myocardial injury, most commonly TnI, TnT, or CK-MB. If no biomarker of myocardial injury is detected, the patient may be considered to have experienced UA; if these biomarkers are present, NSTEMI is the diagnosis (Anderson et al, 2007).

Patients with acute chest pain but without persistent ST-segment elevation (ie, patients with UA or NSTEMI) have transient ST-segment depression or T-wave inversion, flat T waves, pseudonormalization of T waves, or no ECG changes at presentation. The initial strategy for UA or NSTEMI is to alleviate ischemia and symptoms and to monitor serial ECGs and markers of myocardial necrosis (Bassand et al, 2007).

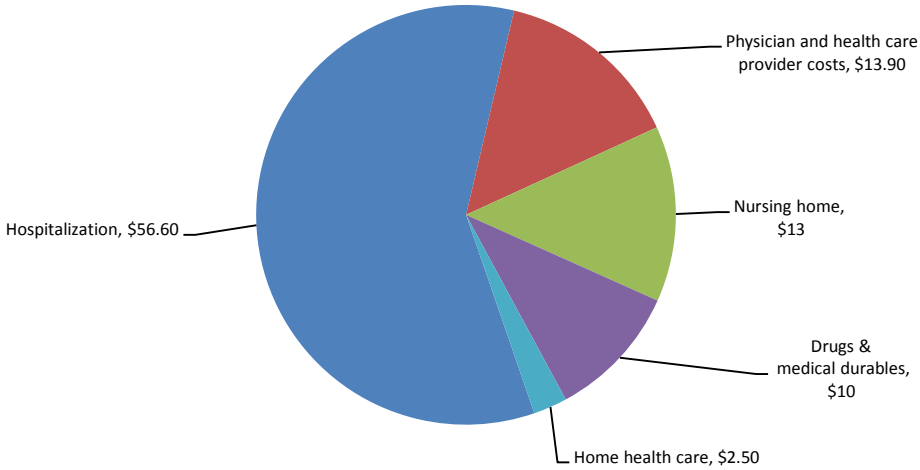
Common initial symptoms of UA/NSTEMI are chest pain, arm pain, lower jaw pain, shortness of breath, and diaphoresis or anginal equivalents, such as dyspnea or extreme fatigue (Anderson et al, 2007).

Typical acute chest pain and persistent (>20 min) ST-segment elevation are characteristic of STEMI and generally reflect a complete coronary artery occlusion that leads to cardiac myocyte death.

2.2.1.4 Societal and Economic Burden

ACS, a manifestation of CHD, describes a set of life-threatening, acute ischemic cardiac conditions, encompassing STEMI, NSTEMI, or UA (Etemad and McCollam, 2005; Lloyd-Jones et al, 2010). According to the AHA statistics, CHD places a substantial economic burden on the US health care system. Direct costs in the US for CHD, which consist primarily of costs for ACS, were estimated to reach $96 billion in 2010. The costs are driven primarily by hospitalizations, as shown in the following figure (Lloyd-Jones et al, 2010). Indirect costs of CHD are also high and estimated at $81.1 billion, bringing the total cost for CHD-related care to $177.1 billion.

FIGURE 2-4: Direct Costs of CHD in 2010 ($, Billions). Adapted from *Circulation.* 2010;121:e46-e215.



For ACS specifically, the annual costs of care in the first year after diagnosis are very high, at approximately $30,000 per patient (Menzin et al, 2008; Etemad and McCollam, 2005; McCollam and Etemad, 2005). The costs are primarily driven by hospitalizations. The annual number of hospitalizations estimated in 2006 ranged from 733,000 discharges (primary diagnosis of ACS) to 1,365,000 discharges (secondary diagnosis of ACS) (Lloyd-Jones et al, 2010). High re-hospitalization rates are also a significant cost driver. Several retrospective studies using managed care databases have described similar patterns of initial costs of ACS.

- An analysis using a multiemployer claims database of 16,321 patients hospitalized for ACS found per-patient expenditures of the initial hospitalization for ACS to be approximately $23,000 (Menzin et al, 2008). About 20% of the patients were re-hospitalized within 1 year; the cost of re-hospitalization averaged $28,500. The total first-year costs of care were $32,500 with approximately 60% of these costs due to re-hospitalization, followed by outpatient costs (24%) and pharmacy utilization (15%).

- In the first year following a new diagnosis of ACS (n=13,731), Etemad and McCollam (2005) found the total cost of ACS incurred by a health plan averaged $2312 per patient-month. Hospitalization costs accounted for 71% of total costs.

- Berenson et al (2010) found similar high rates of re-hospitalization in patients with newly diagnosed ACS in a small regional health plan (32% of 11,266 patients) and a large national representative managed care database (34% of 97,177 patients).

Revascularization procedures are also common and costly in the first year after ACS diagnosis:

- McCollam and Etemad (2005) found that approximately 50% of patients with ACS (6929 of 13,731 patients) had a revascularization procedure during the first year after diagnosis. Total health care costs for these patients averaged

$30,402 per patient. The cost per patient varied by type of procedure: $25,411 for patients undergoing PCI and $43,355 for CABG patients. Hospitalizations accounted for 77% ($161.7 million) of total health plan expenditures with the mean inpatient length of stay of 7.4 days.

- In the study by Berenson et al (2010), revascularization procedures including CABG, PCI (with or without stent placement), and length of stay during ACS-related rehospitalization were the strongest predictors of increased charges after multivariate analysis was performed.

Mortality and Health-related Quality of Life

In addition to the substantial economic burden, ACS results in significant morbidity and mortality, accounting for half of all deaths due to CV disease (Kolansky, 2009). In addition, survivors have significant morbidity and reduced HRQoL; up to 30% of discharged patients are re-hospitalized within 6 months despite use of strategies to reduce ACS-related morbidity and mortality. For example, ACS patients evaluated 3 months after discharge from the hospital had a significant decrease in physical functioning, general health, vitality, and PCS of the Health Survey Short Form 36-item (SF-36) compared with their baseline HRQoL at the initial hospitalization (Failde and Soto, 2006). For patients who underwent revascularization during the 3-month follow-up period, the decline in PCS was smaller than that for patients who did not have revascularization.

ACS also has an impact on work performance and associated HRQoL. Using the Work Performance Scale (a 6-item scale that assesses job-related changes due to health, ability to and time required to perform tasks, and interpersonal relationships), a survey was created for and conducted with patients with previously diagnosed ACS (490 respondents) (Ellis et al, 2005). Patients who were currently employed reported a high level of work performance (mean score 4.6 of 5.0); higher perceived disease severity, higher age, and lower PCS-8 scores were associated with lower work performance scores.

2.2.2 Approaches to Treatment

ACS is a spectrum of conditions characterized by acute myocardial oxygen deprivation causing ischemic chest pain, and this spectrum includes UA, NSTEMI, and STEMI (Grech and Ramsdale, 2003). Multiple assessments and drug therapies are used in the treatment of ACS: continual risk assessment, anti-ischemic therapy, antithrombotic therapy, and antiplatelet therapy. The latter 3 therapies are key components of both medical management and invasive treatment approaches for UA/NSTEMI and STEMI (Anderson et al, 2007), and fibrinolytic therapy is a component of the medical management approach for STEMI (Antman et al, 2008).

Risk Assessment

Risk assessment of patients with UA/NSTEMI or STEMI is used to guide treatment because their risk of nonfatal ischemic events and cardiac death can differ greatly (Anderson et al, 2007; Antman et al, 2004). Examples of risk-stratification models in which this multivariable approach are used is the TIMI risk models for UA/NSTEMI (Antman et al, 2000) and STEMI (Morrow et al, 2000).

TIMI risk scores are based on 7 variables for UA/NSTEMI (Antman et al, 2000) and 10 variables for STEMI (Morrow et al, 2000). TIMI risk scores for UA/NSTEMI are based on the following factors: age of 65 years or more, 3 or more risk factors for CAD, previous coronary stenosis of at least 50%, ST-segment deviation on ECG, 2 or more anginal events during the previous 24 hours, ASA use in the previous week, and elevated serum cardiac biomarkers (Antman et al, 2000). TIMI risk scores for STEMI are based on the following factors: age of at least 75 years, Killip class II-IV, heart rate exceeding 100 bpm, anterior MI or left bundle branch block (LBBB), systolic blood pressure <100 mm Hg, time to thrombolytic >4 hours, weight <67 kg, prior angina, diabetes mellitus, and hypertension (Morrow et al, 2000).

Medical Management and Invasive Treatment for ACS

Patients with ACS receive aggressive medical treatment initially (Anderson et al, 2007), but depending on their condition, patients are triaged for implementation of an initial invasive strategy or an initial conservative strategy (Anderson et al, 2007). The initial invasive strategy consists of PCI and/or CABG; angiography is often begun within 4 to 24 hours of admission (Antman et al, 2004). In the initial conservative strategy, patients with ACS undergo invasive measures only if medical therapy fails as indicated by refractory angina or angina at rest or if ischemia is evident (Anderson et al, 2007).

Invasive treatment for ACS includes the use of PCI, which consists of multiple percutaneous methods (eg, standard balloon angioplasty, stenting of coronary arteries, and atheroablation [atherectomy, thrombectomy, laser angioplasty]) designed to restore perfusion to the myocardial region directly affected by the infarct or ischemia (Anderson et al, 2007).

Stenting of a coronary artery can be accomplished during PCI for ACS and has been shown to reduce the risk of acute and late vessel reocclusion (Anderson et al, 2007; Wilson et al, 2001). Two types of stents available for use in the US are the

BMS and the DES (Anderson et al, 2007; King et al, 2008). Dual antiplatelet therapy (ASA and a $P2Y_{12}$ inhibitor) is currently recommended for varying lengths of time, depending on the type of stent used (Anderson et al, 2007; Kushner et al, 2009; Levine et al, 2011).

CABG surgery is a second type of invasive treatment used to treat ACS. In this procedure, a blood vessel such as the internal mammary artery is removed from its original site within the patient and used to bypass the occluded coronary artery and restore blood flow (Anderson et al, 2007).

2.2.2.1 Nondrug and Drug Treatment Options

Nondrug Treatment Options

Nondrug treatment options for patients with ACS are designed to aid in secondary prevention of CV events. To treat important risk factors that include hypertension, dyslipidemia, obesity, and diabetes mellitus, lifestyle modifications such as smoking cessation, weight loss, increased physical activity (when appropriate), and dietary changes (eg, reduction in dietary saturated fat, cholesterol, and salt) are recommended by the ACC and AHA (Smith et al, 2011; Anderson et al, 2007).

Drug Treatment Options

Fibrinolytic/Anti-ischemic/Antithrombotic Therapy

The purpose of fibrinolytic therapy is to achieve reperfusion of the myocardium as rapidly as possible to minimize the total ischemic time (Antman et al, 2004; Antman et al, 2008). Fibrinolytic drugs used in the treatment of STEMI are plasminogen activators: streptokinase, alteplase, reteplase, and tenecteplase (Antman et al, 2004). Fibrinolytic therapy is recommended for patients with STEMI who present to a hospital that is unable to provide expert, prompt primary PCI within 90 minutes of the patients' arrival (Antman et al, 2008). The fibrinolytic agents are to be given within 30 minutes of patient presentation (Antman et al, 2008). In contrast, fibrinolytic therapy is not recommended for the treatment of UA/NSTEMI (Anderson et al, 2007).

Anti-ischemic therapy is designed to relieve ischemia and involves the use of multiple classes of drugs: nitrates (typically nitroglycerin), morphine sulfate, beta-adrenergic blockers, ACE-Is, ARBs, and aldosterone receptor antagonists (Anderson et al, 2007).

The purpose of antithrombotic therapy is to alter the disease process and progression to myocardial (re)infarction or death in most of the patients whose ACS is due to thrombosis on a plaque (Anderson et al, 2007). The most effective antithrombotic therapy consists of ASA, an anticoagulant (eg, unfractionated heparin, low-molecular-weight heparins [enoxaparin {Lovenox®} or dalteparin {Fragmin®}], a direct thrombin inhibitor [bivalirudin {Angiomax®}], and a factor Xa inhibitor [fondaparinux {Arixtra®}]) and an antiplatelet agent (Anderson et al, 2007). The intensity of antithrombotic therapy is tailored to the patient's risk.

Antiplatelet Therapy

The types of antiplatelet agents used in treating ACS are ASA, $P2Y_{12}$ receptor antagonists (thienopyridines [ticlopidine, clopidogrel, and prasugrel {Effient™, Eli Lilly and Company and Daiichi Sankyo, Inc}], a cyclopentyltriazolopyrimidine [ticagrelor {BRILINTA™, AstraZeneca LP}]), and GP IIb/IIIa inhibitors (abciximab [Reopro®, Eli Lilly and Company], eptifibatide [Integrilin®, Schering Plough], and tirofiban [Aggrastat®, Medicure Pharma]).

ASA is associated with some of the strongest evidence about the long-term prognostic effects of therapy in patients with CAD (Anderson et al, 2007). ASA acts by irreversibly inhibiting cyclo-oxygenase 1 in platelets, an event that blocks thromboxane A_2 production; thus, platelet aggregation promoted by this pathway is reduced (Anderson et al, 2007). Regardless of differences in study design, trials of ASA in patients with ACS have consistently shown a beneficial effect of this drug as compared to placebo (Anderson et al, 2007; Antman et al, 2008).

$P2Y_{12}$ receptor antagonists consist of the thienopyridines (ticlopidine, clopidogrel, and prasugrel) and a cyclopentyltriazolopyrimidine (BRILINTA). The thienopyridines inhibit platelet activation and aggregation by irreversibly binding to the $P2Y_{12}$ type of ADP receptors on the surface of platelets and thus blocking ADP-mediated activation of the GP IIb/IIIa receptor complex. Active metabolites of the prodrugs clopidogrel and prasugrel are responsible for their antiplatelet effects (Plavix Prescribing Information and Effient Prescribing Information), but ticlopidine does not require metabolism for its platelet activity (ticlopidine prescribing information). Each $P2Y_{12}$ receptor antagonist available in a tablet formulation that is administered orally; however, the ACS-related indications and dosages of each agent differ.

Ticlopidine is indicated as adjunctive therapy with ASA to decrease the incidence of subacute stent thrombosis in patients undergoing successful implementation of a coronary stent (ticlopidine prescribing information). Clopidogrel is indicated for UA/NSTEMI that is medically managed or managed by coronary revascularization, STEMI, a history of a recent MI or

recent stroke, and established peripheral artery disease (Plavix Prescribing Information). Prasugrel is indicated to reduce the rate of thrombotic CV events (including stent thrombosis) in patients with ACS (UA, NSTEMI, and STEMI) who are to be managed with PCI (Effient Prescribing Information).

BRILINTA is indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS (UA, NSTEMI, and STEMI). BRILINTA has been shown to reduce the rate of a combined endpoint of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. BRILINTA has been studied in ACS in combination with ASA. Maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of ASA above 100 mg daily (BRILINTA Prescribing Information).

The GP IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) antagonize the platelet GP IIb/IIIa receptors and thus prevent platelet aggregation (ReoPro Prescribing Information; Aggrastat Prescribing Information; Integrilin Prescribing Information).

2.2.2.2 Place of BRILINTA in Therapy

BRILINTA is a selective and reversibly binding $P2Y_{12}$ ADP-receptor antagonist. BRILINTA is indicated to reduce the rate of thrombotic CV events in patients with ACS (UA, NSTEMI, STEMI). BRILINTA has been shown to reduce the rate of a combined endpoint of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis (BRILINTA Prescribing Information).

BRILINTA has been studied in ACS in combination with ASA. Maintenance doses of ASA above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of ASA above 100 mg daily. (BRILINTA Prescribing Information). The efficacy of ticagrelor was evaluated in the PLATO trial, a multinational, randomized, double-blind study that compared ticagrelor to clopidogrel for the prevention of CV events in 18,624 patients with UA, NSTEMI, or STEMI (Wallentin et al, 2009a).

- Patients who received ticagrelor had a 16% RRR in the composite of death from vascular causes, MI, or stroke compared to those receiving clopidogrel ($p<0.001$; 1.9% ARR, NNT=54) (Wallentin et al, 2009a; Wallentin et al, 2009, presentation).
- Lower event rates were observed in the ticagrelor group for the composite endpoint of death from any cause, MI, or stroke (10.2% vs. 12.3% for clopidogrel, 16% RRR, $p<0.001$), as well as for the individual endpoints of MI and CV death (16% RRR, $p=0.005$ and 21% RRR, $p=0.001$, respectively) (Wallentin et al, 2009a).
- A wide range of demographic, concurrent baseline medications and other treatment differences were examined for their influence on outcome. Most of the analyses show effects consistent with the overall results, but there are 2 marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of ASA. In the North American subgroup, ticagrelor was numerically inferior to clopidogrel. While this could be due to chance, retrospective analyses supports the possibility that this finding is reliable and due to ASA maintenance dose. Despite the need to treat such results cautiously, there appears to be good reason to restrict ASA maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of ticagrelor (BRILINTA Prescribing Information).
- Results of subgroup analyses of the PLATO trial in patients with a planned invasive treatment strategy were generally consistent with those of the overall trial population (Wallentin et al, 2009a). The occurrence of the composite efficacy endpoint in these patients (n=13,408) was significantly lower in the ticagrelor group at Day 360 than in the clopidogrel group on the same day (9.0% vs. 10.7%, respectively; $p=0.0025$) (Cannon et al, 2010).
- Stent thrombosis rates differed among ticagrelor- and clopidogrel-treated patients for whom an invasive strategy was planned.
    - Definite stent thrombosis occurred in fewer patients in the ticagrelor group (n=62, 1.3%) than in the clopidogrel group (n=97, 2.0%; $p=0.0054$).
    - Compared with patients in the clopidogrel group, fewer patients in the ticagrelor group experienced definite or probable stent thrombosis: 142 (3.0%) vs. 104 (2.2%), respectively ($p=0.0142$).
    - Similarly, total (ie, definite, probable, or possible) stent thrombosis was seen in fewer patients in the ticagrelor group (n=132 [2.8%]) than in the clopidogrel group (n=179 [3.8%], $p=0.0068$).

- In the genetic subanalysis of PLATO, the occurrence of the primary endpoint of PLATO was lower with ticagrelor compared to clopidogrel (Wallentin et al, 2010).
    - A fewer number of events from the primary efficacy endpoint were seen with ticagrelor than clopidogrel in patients with any CYP2C19 LOF allele (HR: 0.77; 95% CI: 0.60-0.99; p=0.0380). A similar trend was also observed in patients without CYP2C19 LOF allele (HR: 0.86; 95% CI: 0.74-1.01; p=0.0608; p-value interaction=0.46). In the ticagrelor group, the rate of the primary efficacy endpoint was similar in patients with (8.6% per year) or without (8.8% per year) any LOF allele during the entire treatment period.
    - A comparison of ticagrelor versus clopidogrel at 30 days showed numerically fewer composite events with ticagrelor (4.1%) than clopidogrel (5.7% [HR: 0.73; 95% CI: 0.52-1.03; p=0.078]) in patients with any LOF allele but similar results between treatment groups in patients without any LOF allele (3.8% in both groups).
- The rates of major bleeding in the PLATO study were not different between the 2 treatment groups. Ticagrelor was associated with a higher rate of nonCABG major bleeding (Wallentin et al, 2009a).
- There was no difference between treatment groups in the overall rate of fatal bleeding; however, within the fatal bleeding category, the rate of fatal nonintracranial bleeding was greater in the clopidogrel group and the rate of fatal intracranial bleeds was greater in the ticagrelor group (Wallentin et al, 2009a).
- In the genetic subanalysis of PLATO, no variation in bleeding rates in relation to CYP2C19 or ABCB1 polymorphisms was observed in the ticagrelor group (Wallentin et al, 2010). Patients receiving clopidogrel who had any CYP2C19 GOF allele had significantly higher rates of PLATO-defined major bleeding compared to those without any GOF or LOF alleles (p=0.022).
- Dyspnea was reported in 13.8% of ticagrelor-treated and 7.8% of clopidogrel-treated patients; 0.9% of patients in the ticagrelor group and 0.1% of patients in the clopidogrel group discontinued the study drug because of dyspnea (p<0.001 for both comparisons) (Wallentin et al, 2009a).
- Holter monitoring of a subgroup of patients in the PLATO trial showed that those in the ticagrelor group had a higher incidence of ventricular pauses in the first week, but not at Day 30, when compared to patients in the clopidogrel group. Pauses were rarely associated with symptoms.
- Laboratory test changes included greater increases in serum uric acid levels in the ticagrelor group compared to the clopidogrel group at 1 and 12 months of treatment (14%-15% in the ticagrelor group vs. 7% in the clopidogrel group; p<0.001 both time points; 7%-8%). At 1 month after the end of treatment, there was no difference between treatment groups with regard to changes in uric acid levels (p=0.56).
- Although ticagrelor-treated patients experienced a greater change in serum creatinine levels from baseline (10%-11%) at 1 and 12 months of therapy (p<0.001 for both) than clopidogrel-treated patients (8%-9%), the difference between groups was not statistically significant by 1 month after the end of treatment.

Considerations for Antiplatelet Therapy

As stated earlier, platelet activation and aggregation are important contributors to the pathophysiology of ischemia in ACS (Collet and Montalescot, 2009). Clinical trials have shown antiplatelet agents such as $P2Y_{12}$ receptor antagonists are crucial to antithrombotic therapy for ACS; however, extensive evidence indicates interpatient variability (even nonresponsiveness) to the $P2Y_{12}$ receptor antagonist clopidogrel (Angiolillo et al, 2007). The pathways responsible for the diminished responsiveness or nonresponsiveness are not well characterized, but proposed mechanisms include decreased intestinal absorption, polymorphisms in CYP enzymes (especially CYP2C19 [Mega et al, 2009]), and polymorphisms in $P2Y_{12}$ receptors (Collet and Montalescot, 2009). The clopidogrel prescribing information includes a boxed warning related to diminished effectiveness in 2C19 poor metabolizers and the use of testing to identify the 2C19 gentotype (Plavix Prescribing Information).

Commercial assays for genetic phenotyping are available from both research and clinical laboratories. Cross validation of the techniques used and their reliability, specificity, and reproducibility are limited. While results of commercial assays can be applied, they are not available in the acute phases of patient care. Point-of-care assays for the common CYP2C19 polymorphisms are not available at this time. An important patient care issue relates to the cost for these tests, which are usually not reimbursed by major payers. Alternatives to genetic testing focus on platelet function assays that can measure the effect of ADP or P2Y12 activation on platelet aggregation, receptor expression, or the level of intracellular molecules (eg, vasodilator-stimulated phosphoprotein phopsphorylation), thereby directly or indirectly measuring the platelet inhibitory effect of clopidogrel (ie, clopidogrel responsiveness or on-treatment reactivity) (Holmes et al, 2010).

The gold standard of platelet function assays is turbidometric platelet aggregometry. With this in vitro assay, platelet aggregation in plasma is measured by using light transmission. The ability of thienopyridines to alter platelet responsiveness has been assessed in this assay. Although results of clinical studies have suggested that greater responsiveness to antiplatelet therapy in platelet function assays is correlated with improved patient outcomes, the following limitations in these assays have prevented their use in current clinical practice:

- Difficulty in data interpretation and application of findings because of inconsistency in the assays, agonists, cut-off values, and patient populations in various studies,
- Absence of a standard definition of platelet resistance,
- Absence of a standard assay,
- Variability in methods used in different platelet function assays.

Currently, the ACCF/AHA does not recommend the routine use of platelet function or genetic testing. (Levine et al, 2011; Wright et al, 2011; Holmes et al, 2010; Abraham et al, 2010). These types of testing may be considered in patients at risk for poor outcomes or if results may alter management (Levine et al, 2011; Holmes et al, 2010). Patients treated with clopidogrel with high platelet reactivity, treatment with alternative agents, such as prasugrel or ticagrelor, might be considered (Levine et al, 2011).

2.2.2.3 Ancillary Disease or Care Management Intervention Strategies

Not applicable

2.2.2.4 Expected Outcomes of Therapy

The PLATO trial compared ticagrelor to clopidogrel for the prevention of vascular events and death in patients with ACS (Wallentin et al, 2009a; Wallentin et al, 2009, presentation). At 12 months, 9.8% of ticagrelor-treated patients and 11.7% of clopidogrel-treated patients experienced an event from the composite primary endpoint (HR: 0.84; 95% CI=0.77-0.92; p<0.001; 1.9% ARR; NNT=54). The RRR in the primary endpoint when ticagrelor was compared with clopidogrel was 16% (Wallentin et al, 2009a, BRILINTA Prescribing Information). The difference between treatments was driven by CV death and MI with no difference in stroke. Within the initial 30 days of therapy, a difference in treatment effect was observed and persisted throughout the study.

The data on the primary endpoint were consistent in the analysis of all prespecified subgroups, with 3 exceptions. The benefit of ticagrelor appeared to be attenuated in patients with body weight below the median for their sex (p=0.04 for the interaction). In patients not taking lipid-lowering drugs (p=0.04 for the interaction) and in patients enrolled from North America (n=1814; p=0.045 for the interaction), no treatment advantage was shown for ticagrelor.

Results in the subgroup of patients for whom invasive therapy was planned at randomization (principal secondary endpoint) were consistent with the overall results: the rate of occurrence for a primary event was lower in the ticagrelor group compared to the clopidogrel group (8.9% vs. 10.6%, respectively; 16% RRR; p=0.003).

Lower event rates were observed in the ticagrelor group for the composite endpoint of death from any cause, MI, or stroke (10.2% vs. 12.3% for clopidogrel; 16% RRR; p<0.001), as well as for the individual endpoints of MI and death from vascular causes (16% RRR; p=0.005 and 21% RRR; p=0.001, respectively). The occurrence of stroke was not statistically different between groups (ticagrelor, 1.5% vs. clopidogrel, 1.3%; p=0.22). Treatment with ticagrelor was associated with an RRR of 22% in the rate of death from any cause at 1 year (HR: 0.78 [0.69-0.89]; p<0.001).

Safety analyses showed that the rates of major bleeding were not different between the 2 treatment groups (11.6% for the ticagrelor-treated group and 11.2% for the clopidogrel-treated group; p=0.43). When the occurrence of major bleeding events was analyzed on the basis of the TIMI bleeding criteria, the rates of major bleeding events were not different between the ticagrelor and clopidogrel treatment groups (7.9% and 7.7%, respectively; p=0.57). There was no difference between treatment groups in the overall rate of fatal bleeding (0.3% for both groups; p=0.66). Within the category of fatal bleeding, the rate of fatal nonintracranial bleeding was greater in the clopidogrel treatment group (21 [0.3%] for clopidogrel vs. 9 [0.1%] for ticagrelor; p=0.03), whereas a greater number of fatal intracranial bleeds occurred in the ticagrelor group (11 [0.1%] vs. 1 [0.01%] for clopidogrel; p=0.02). Ticagrelor was associated with a higher rate of nonCABG-related major bleeding (4.5% vs. 3.8%; p=0.03). Results for the primary bleeding endpoint in the prespecified subgroups were consistent with the overall population, with the exception of patients with a body-mass index ≥30 kg/m^2 (p=0.05 for the interaction).

Dyspnea, another secondary safety endpoint, occurred in 13.8% of ticagrelor-treated patients and 7.8% of clopidogrel-treated patients; 0.9% of ticagrelor-treated patients and 0.1% of clopidogrel-treated patients discontinued study treatment as a result (p<0.001 for both comparisons).

Holter monitoring was performed in a subgroup of patients. The incidence of ventricular pauses ≥3 seconds during the first week was significantly higher in the ticagrelor group (84/1451 [5.8%]) than in the clopidogrel group (51/1415 [3.6%]; p=0.01); however, there was no difference between the 2 groups at 30 days: 21/985 (2.1%) for the ticagrelor group and 17/1006 (1.7%; p=0.52) for the clopidogrel group.

Laboratory test changes included greater increases in serum uric acid levels in the ticagrelor group compared to the clopidogrel group at 1 and 12 months of treatment (14%-15% in the ticagrelor group vs. 7% in the clopidogrel group; p<0.001 for both time points). At 1 month after the end of treatment, there was no difference between treatment groups with regard to changes in uric acid levels (p=0.56). Ticagrelor-treated patients experienced a greater change in serum creatinine levels from baseline (10%-11%) at 1 and 12 months of therapy (p<0.001 for both time points) than clopidogrel-treated patients (8%-9%). The difference between groups was not statistically significant by 1 month after the end of treatment (+10% for both groups; p=0.59).

2.2.2.5 Other Drug Development or Postmarketing Obligations

Risk Evaluation and Mitigation Strategy

A BRILINTA REMS has been developed to communicate certain risks. The goals of the BRILINTA REMS are:

- To inform health care professionals and patients of the serious risks associated with BRILINTA, particularly the increased risk of bleeding.
- To inform health care professionals and patients that the daily maintenance dose of ASA, coadministered with BRILINTA, should not exceed 100 mg.

The BRILINTA REMS includes a Medication Guide (for patients) and a Communication Plan, including a Dear Healthcare Professional Letter and a Professional Organization Letter (for health care professionals). Additional information can be found at the following site: http://www.brilintarems.com.

PEGASUS-TIMI

The PEGASUS-TIMI 54 study will investigate if treatment with ticagrelor and ASA will further reduce the risk of subsequent CV events compared to ASA alone in patients with a prior MI (US National Institutes of Health, 2011). The study will examine the long-term efficacy and safety of ticagrelor in patients who have sustained a heart attack from 1 to 3 years prior to enrollment. The study began patient enrollment during the fourth quarter of 2010 and is estimated to complete in the first quarter of 2014.

PEGASUS-TIMI 54 is a randomized, double-blind, 3-arm, parallel-group, international, multicenter study of approximately 21,000 patients in over 30 countries. The study is event-driven, and the minimum treatment period is 12 months. Patients will be randomized to ticagrelor 60 or 90 mg twice daily or placebo. In addition to ticagrelor or placebo, patients will take once daily, concomitant ASA therapy (75 to 150 mg). The primary efficacy endpoint for the PEGASUS-TIMI 54 study is the time to first occurrence of any CV event including CV death, nonfatal MI, or nonfatal stroke.

2.2.3 Relevant Treatment Guidelines

ACCF/AHA Guidelines

The ACCF/AHA Task Force on Practice Guidelines was formed to make recommendations regarding the diagnosis and treatment of patients with CV disease. Experts in the field are selected to undertake a comprehensive review of the evidence for management and/or prevention of a given condition. The Task Force has compiled several guidelines addressing treatment of ACS (Anderson et al, 2007; Kushner et al, 2009; Wright et al, 2011; Levine et al, 2011; Hillis et al, 2011; Smith et al, 2011). A summary of the use of oral antiplatelet agents from these guidelines are presented below.

In these guidelines, the level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales. The weight of the evidence is ranked highest (A) if the data were derived from multiple, large, randomized clinical trials or meta-analyses or ranked intermediate (B) if the data were derived from a single randomized trial or nonrandomized studies. A lower rank (C) is given when expert consensus, case studies, or standard of care are the primary basis for the recommendation. The customary ACCF/AHA classifications I, II, and III are used to summarize both the evidence and expert opinion and provide final recommendations. Class I indicates that there is evidence and/or general consensus that a given procedure or treatment is useful and effective. Class IIa indicates that despite conflicting evidence, a treatment or procedure is reasonable. Class IIb indicates that despite greater conflicting evidence, a treatment or procedure may be considered. Class III indicates a procedure or treatment is not useful or effective and in some cases may be harmful. Clinicians are encouraged to review the definitions for classifications and levels of evidence in the full-text documents.

Key recommendations addressing the use of oral antiplatelet agents in ACS are provided below.

Antiplatelet agents are recommended in patients with ACS who are managed either invasively or noninvasively. According to the ACCF/AHA guidelines for patients with UA/NSTEMI, which were published prior to the approval of ticagrelor in the United States, ASA (IA) and clopidogrel (IB) should be initiated as soon as possible in patients with UA or NSTEMI who are managed noninvasively (Anderson et al, 2007; Anderson et al, 2011; Wright et al, 2011).

In ACS patients undergoing PCI with stenting, the ACCF/AHA PCI guideline recommends ASA in addition to a loading dose of a $P2Y_{12}$ receptor inhibitor (clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg) prior to PCI (IA).The recommended ASA dose prior to PCI is 81-325 mg for patients who were previously receiving ASA, and 325 mg for patients not previously receiving ASA (IB). (Levine et al, 2011)

In patients referred for elective CABG, the ACCF/AHA recommends that clopidogrel and ticagrelor be discontinued for at least 5 days before surgery (IB) and prasugrel for at least 7 days (IC) to limit blood transfusions. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications (IB). In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued. (IIbC) (Hillis, 2011)

Secondary prevention guidelines in patients after ACS or PCI with stent placement include combination use of a $P2Y_{12}$ inhibitor and ASA (IA). For patients receiving a BMS or DES during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months (IA). After PCI, it is reasonable to use ASA 81 mg per day in preference to higher maintenance doses (IIaB). Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of DES (IIbC). If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable (IIaC). Patients should be counseled on the importance of compliance with dual antiplatelet therapy and that therapy should not be discontinued before discussion with their cardiologist (IC) (Levine et al, 2011; Smith et al, 2011).

ACCP Guidelines

ACCP issued an update to the evidence-based clinical practice guidelines for the secondary prevention of CV disease in February 2012 (Vandvick et al, 2012). ACCP classifies recommendations into 2 levels: strong and weak. A strong recommendation is classified as Grade 1. A weak recommendation is classified as Grade 2 and is given when the benefits and risks/burdens are finely balanced, or if uncertainty exists about the magnitude of the benefits and risks/burdens. Grade 1 and 2 recommendations are further categorized by quality of evidence: high (grade A); moderate (grade B); and low or very low quality (grade C) (Guyatt et al, 2006). The following is a summary of the pertinent changes to the guidelines related to antiplatelet use and ticagrelor.

For patients in the first year after an ACS who have not undergone PCI, ACCP guidelines recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose ASA 75-100 mg daily or clopidogrel 75 mg daily plus low-dose ASA 75-100 mg daily) over single antiplatelet therapy (Grade 1B). In addition, the guidelines suggest ticagrelor 90 mg twice daily plus low-dose ASA over clopidogrel 75 mg daily plus low-dose ASA (Grade 2B) (Vandvick et al, 2012).

For patients in the first year after an ACS who have undergone PCI with stent placement, ACCP guidelines recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose ASA 75-100 mg daily, clopidogrel 75 mg daily plus low-dose ASA, or prasugrel 10 mg daily plus low-dose ASA) over single antiplatelet therapy (Grade 1B). In addition, the guidelines suggest ticagrelor 90 mg twice daily plus low-dose ASA over clopidogrel 75 mg daily plus low-dose ASA (Grade 2B) (Vandvick et al, 2012).

2.3 EVIDENCE FOR PHARMACOGENOMIC TESTS AND DRUGS

Not applicable

SECTION 3.0 Supporting Clinical Evidence

3.1 SUMMARIZING KEY CLINICAL STUDIES

3.1.1 PUBLISHED & UNPUBLISHED STUDIES FOR LABELED INDICATIONS

Phase III Studies

Wallentin L, Becker RC, Budaj A, et al for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009a;361:1045-1057.

Wallentin L, Becker RC, Budaj A, et al for the PLATO Investigators. Supplementary appendix. *N Engl J Med.* 2009b;361:1045-1057. Available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0904327/suppl_file/nejm_wallentin_1045sa1.pdf. Accessed July 20, 2011.

James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral $P2Y_{12}$ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J.* 2009;157:599-605.

Wallentin L, Becker RC, Budaj A, et al for the PLATO investigators. Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results of the PLATelet inhibition and patient Outcomes (PLATO) trial [presentation]. Presented at: European Society of Cardiology; August 29-September 2, 2009; Barcelona, Spain.

Study dates: Recruitment lasted from October 2006 through July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study locations: 862 centers in 43 countries, including the United States (Wallentin et al, 2009a; Wallentin et al, 2009b). The PLATO trial was registered with the web site www.clinicaltrials.gov (http://www.clinicaltrials.gov/ct2/show/NCT00391872?term=acute+coronary+syndrome+AND+AstraZeneca&rank=5).

Study objective: To compare ticagrelor to clopidogrel for the prevention of vascular events and death in patients with ACS (UA, NSTEMI, or STEMI) (Wallentin et al, 2009a)

Study design: The study of Platelet Inhibition and Patient Outcomes (PLATO) was a multinational, randomized, double-blind, double-dummy, parallel-group, event-driven Phase III study that compared ticagrelor plus ASA to clopidogrel plus ASA for the prevention of CV events in patients with ACS (Wallentin et al, 2009a; James et al, 2009). A randomization schedule blocked by site was used to randomly assign patients in a 1:1 ratio to either ticagrelor or clopidogrel treatment. Randomization was accomplished within 24 hours of cardiac ischemic symptoms but before PCI (James et al, 2009).

Inclusion and exclusion criteria: Eligible for inclusion were patients hospitalized with documented ACS (cardiac ischemic symptoms due to atherosclerosis of ≥10 minutes duration at rest) within the previous 24 hours, with or without ST-segment elevation (James et al, 2009; Wallentin et al, 2009a). Additional inclusion and exclusion criteria are shown in the following tables.

TABLE 3-1: PLATO Inclusion Criteria. Adapted from *Am Heart J*. 2009;157:602.

Hospitalized for ACS With or Without ST-segment Elevation, With Onset During the Previous 24 Hours		
***AND* ≥2 of the following:**		***OR* either of the following:**
1. ST-segment changes on ECG indicating ischemia 2. Positive biomarker indicating myocardial necrosis 3. One of the following: a. ≥60 years of age b. Previous MI or CABG c. CAD with ≥50% stenosis in ≥2 vessels d. Previous ischemic stroke, TIA (hospital-based diagnosis), carotid stenosis (≥50%), or cerebral revascularization e. Diabetes mellitus f. Peripheral artery disease g. Chronic renal dysfunction		1. Persistent ST-segment elevation ≥1 mm (not known to be pre-existing or due to a co-existing disorder) in ≥2 contiguous leads plus primary PCI planned 2. New LBBB plus primary PCI planned

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

TABLE 3-2: Key PLATO Exclusion Criteria. Adapted from *Am Heart J*. 2009;157:602.

Drug-related	• Contraindication to clopidogrel or other reason that study drug should not be administered • Oral anticoagulation therapy that cannot be stopped • Fibrinolytic therapy planned or within the previous 24 hours • Concomitant oral or IV therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers
Treatment-related	• Index event is an acute complication of PCI • PCI after index event and before first study dose
Medical	• Increased risk of bradycardiac events • Dialysis required • Known clinically important thrombocytopenia or anemia[a] • Any other condition that may put the patient at risk or influence study results[a]

CYP = cytochrome P450; IV = intravenous; PCI = percutaneous coronary intervention. [a] According to the investigator.

Patients were evaluated at 1, 3, 6, 9, and 12 months after hospital admission and 1 month following discontinuation of study treatment (Wallentin et al, 2009a).

Treatment Arms/Dosing: Patients were randomly assigned to receive one of the following.

- Ticagrelor
  - Patients randomized to ticagrelor received a LD of 180 mg. The maintenance dose of ticagrelor was 90 mg BID.
  - Patients in the ticagrelor treatment arm who were undergoing PCI more than 24 hours after randomization received an additional LD of ticagrelor 90 mg.

- Clopidogrel
  - Patients randomized to clopidogrel who had not received a LD of clopidogrel, or had not been taking clopidogrel or ticlopidine for ≥5 days prior to randomization, received a 300 mg LD of clopidogrel as their first dose. The maintenance dose of clopidogrel was 75 mg QD.
  - Patients in the clopidogrel treatment arm who were undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients also received ASA 75-100 mg daily unless intolerant. In patients who were not previously receiving ASA, the preferred LD was 325 mg. In patients with stents, a dosage of 325 mg QD was permitted for 6 months after stent placement.

- GP IIb/IIIa receptor antagonists and approved parenteral anticoagulants were allowed, but long-term treatment with low-molecular-weight heparin was not recommended. Oral anticoagulation was not permitted.

Endpoints:

Primary Efficacy Endpoint: Time to first occurrence of composite of death from vascular causes, MI, or stroke (death from vascular causes includes CV deaths, cerebrovascular deaths, and any other death for which there was no clearly documented nonvascular cause)

Primary Safety Endpoint: Time to first occurrence of PLATO-defined major bleeding event. Bleeding definitions used in the study are shown in the following table.

TABLE 3-3: Bleeding Definitions Used in the PLATO Trial.[a] Adapted from *Am Heart J*. 2009;157:603.

Bleeding Category	Associated Decrease in Hemoglobin	Transfusion of Whole Blood or PRBCs for Bleeding
Major bleed—life threatening (any of these criteria) Fatal, intracranial, intrapericardial with cardiac tamponade, hypovolemic shock or severe hypotension requiring pressors or surgery	>5 g/dL (3.1 mmol/L)	≥4 units
Major bleed—other (any of these criteria) Significantly disabling (eg, intraocular with permanent vision loss)	3-5 g/dL (1.9-3.1 mmol/L)	2-3 units
Minor bleed	Requires medical intervention to stop or treat bleeding	
Minimal bleed	All others not requiring intervention or treatment	

PRBC = packed red blood cells. [a] If the bleeding event fulfills criteria in more than 1 category, the event was to be assigned to the most severe category.

Results: A total of 18,624 patients (≥18 years of age) were recruited (Wallentin et al, 2009a). Baseline characteristics of the overall study population are presented in the following table.

TABLE 3-4: Select Baseline Characteristics of the PLATO population.[a] Adapted from *N Engl J Med*. 2009a;361:1048.

	Ticagrelor Group n=9333	Clopidogrel Group n=9291
Age (years), median	62.0	62.0
Age ≥75 years, n (%)	1396 (15.0)	1482 (16.0)
Female sex, n (%)	2655 (28.4)	2633 (28.3)
Median body weight, kg (range)	80 (28-174)	80.0 (29-180)
Cardiovascular Risk Factor, n (%)		
Habitual smoker	3360 (36.0)	3318 (35.7)
Hypertension	6139 (65.8)	6044 (65.1)
Dyslipidemia	4347 (46.6)	4342 (46.7)
Diabetes mellitus	2326 (24.9)	2336 (25.1)
Other medical history, n (%)		
MI	1900 (20.4)	1924 (20.7)
Percutaneous coronary intervention	1272 (13.6)	1220 (13.1)
Coronary artery bypass grafting	532 (5.7)	574 (6.2)
Congestive heart failure	513 (5.5)	537 (5.8)
Nonhemorrhagic stroke	353 (3.8)	369 (4.0)
Final diagnosis of acute ACS, n (%)		
ST-elevation MI	3496 (37.5)	3530 (38.0)
Non-ST-elevation MI	4005 (42.9)	3950 (42.5)
Unstable angina	1549 (16.6)	1563 (16.8)
Other diagnosis or missing data[a]	283 (3.0)	248 (2.7)

ACS = acute coronary syndrome; MI = myocardial infarction; n = number of patients. [a] Includes patients with unspecified ACS or no ACS.

- Patients in both groups received study treatment by a median of 11.3 hours after the onset of chest pain.
- The median study drug exposure was 277 days and overall rate of adherence to study medication was 82.8%.
- Forty-six percent of patients in both groups received clopidogrel in the hospital prior to randomization.

Primary Efficacy Endpoint:

- At 12 months, 9.8% of ticagrelor-treated patients versus 11.7% of clopidogrel-treated patients experienced an event from the composite primary endpoint (HR=0.84; 95% CI=0.77-0.92; p<0.001; 1.9% ARR). This represented a 16% RRR in the primary endpoint with ticagrelor compared to clopidogrel. A treatment effect was seen within 30 days and persisted throughout the study period.

- The number needed to treat (NNT) is 54. In other words, treating 54 patients with ticagrelor instead of clopidogrel for 1 year will prevent 1 event of CV death, MI, or stroke (Wallentin, 2009c).

Secondary Efficacy Endpoints:

- Results in the subgroup of patients for whom invasive therapy was planned at randomization (principal secondary endpoint) were consistent with the overall results: the rate of occurrence for a primary event was lower in the ticagrelor group compared to the clopidogrel group (8.9% vs. 10.6%, respectively; 16% RRR; p=0.003) (Wallentin, 2009a).

- Lower event rates were observed in the ticagrelor group for the composite endpoint of death from any cause, MI, or stroke (10.2% vs. 12.3% for clopidogrel; 16% RRR; p<0.001), as well as for the individual endpoints of MI and CV death (16% RRR; p=0.005 and 21% RRR; p=0.001, respectively).

- The occurrence of stroke was not statistically different between groups (ticagrelor 1.5% vs. clopidogrel 1.3%; p=0.22).

- Treatment with ticagrelor was associated with a RRR of 22% in the rate of death from any cause at 1 year (HR=0.78 [0.69-0.89]; p<0.001).

TABLE 3-5: Major Efficacy Endpoints at 12 Months.[a] Adapted from *N Engl J Med*. 2009a;361:1052.

Endpoint	Ticagrelor	Clopidogrel	HR for Ticagrelor (95% CI)	p-value[b]
Primary Endpoint—n/Total N (%)				
Death due to vascular causes, MI, or stroke	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77-0.92)	<0.001[c]
Secondary Endpoints—n/Total N (%)				
Death due to any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77-0.92)	<0.001[c]
Death due to vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81-0.95)	<0.001[c]
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75-0.95)	0.005[c]
Death due to vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69-0.91)	0.001[c]
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91-1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other Events—n/Total N (%)				
Death due to any cause	399/9333 (4.5)	506 (9291) (5.9)	0.78 (0.69-0.89)	<0.001
Death due to causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49-1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74-1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82-1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42-1.44)	0.42
Other arterial thrombotic events	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34-1.08)	0.09
Death from vascular causes, MI, or stroke				
Event rate, Days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77-1.00)	0.045
Event rate, Days 31–360[d]	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70-0.91)	<0.001
Stent Thrombosis—Number of Patients Receiving a Stent/Total Number of Patients				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50-0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59-0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62-0.95)	0.01

MI = myocardial infarction; n = number of events; N = number of patients; TIA = transient ischemic attack. [a] The percentages are Kaplan-Meier estimates of the rate of the endpoint at 12 months. Patients could have ≥1 type of endpoint. Death from vascular causes included fatal bleeding (only traumatic fatal bleeding was excluded from this endpoint category). [b] The p-values were calculated by means of Cox regression analysis. [c] Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy endpoints. [d] Patients with any primary event during the first 30 days were excluded.

- The data on the primary endpoint were consistent in the analysis of 33 prespecified subgroups, with 3 exceptions. The benefit of ticagrelor appeared to be attenuated in patients with body weight below the median for their sex (p=0.04 for the interaction), and in patients not taking lipid-lowering drugs (p=0.04 for the interaction) and patients enrolled from North America (n=1814; p=0.045 for the interaction).

Primary Safety Endpoint

- The rates of major bleeding were not different between the 2 treatment groups (11.6% and 11.2% for the ticagrelor- and clopidogrel-treated groups, respectively; p=0.43).

- When the occurrence of major bleeding events was analyzed according to the TIMI bleeding criteria, the rates were also not different between the ticagrelor and clopidogrel groups (7.9% and 7.7%, respectively; p=0.57).

- There was no difference between treatment groups in the overall rate of fatal bleeding (0.3% for both groups; p=0.66).

- Within the fatal bleeding category, the rate of fatal nonintracranial bleeding was greater in the clopidogrel group (21 [0.3%] vs. 9 [0.1%] for ticagrelor; p=0.03), whereas a greater number of fatal intracranial bleeds occurred in the ticagrelor group (11 [0.1%] vs. 1 [0.01%] for clopidogrel; p=0.02).

- Ticagrelor was associated with a higher rate of PLATO-major bleeding not related to CABG (4.5% vs. 3.8%; p=0.03).

- Results for the primary bleeding endpoint in the prespecified subgroups were consistent with those of the overall population, with the exception of patients with body-mass indices ≥30 kg/m^2 (p=0.05 for the interaction).

TABLE 3-6: Bleeding Endpoints.[a] Adapted from *N Engl J Med*. 2009a; 361:1054.

	Number of Events (%)			
Endpoint	**Ticagrelor n=9235**	**Clopidogrel n=9186**	**Hazard or Odds Ratio for Ticagrelor[b] (95% CI)**	**p-value**
Primary Safety Endpoints				
Major bleeding, PLATO criteria	961 (11.6)	929 (11.2)	1.04 (0.95-1.13)	0.43
Major bleeding, TIMI criteria[c]	657 (7.9)	638 (7.7)	1.03 (0.93-1.15)	0.57
Bleeding requiring red-cell transfusion	818 (8.9)	809 (8.9)	1.00 (0.91-1.11)	0.96
Life-threatening or fatal bleeding, PLATO criteria	491 (5.8)	480 (5.8)	1.03 (0.90-1.16)	0.70
Fatal bleeding	20 (0.3)	23 (0.3)	0.87 (0.48-1.59)	0.66
Non-intracranial bleeding	9 (0.1)	21 (0.3)	—	0.03
Intracranial bleeding	26 (0.3)	14 (0.2)	1.87 (0.98-3.58)	0.06
Fatal	11 (0.1)	1 (0.01)	—	0.02
Nonfatal	15 (0.2)	13 (0.2)	—	0.69
Secondary Safety Endpoints				
Non-CABG-related major bleeding, PLATO criteria	362 (4.5)	306 (3.8)	1.19 (1.02-1.38)	0.03
Non-CABG-related major bleeding, TIMI criteria	221 (2.8)	177 (2.2)	1.25 (1.03-1.53)	0.03
CABG-related major bleeding, PLATO criteria	619 (7.4)	654 (7.9)	0.95 (0.85-1.06)	0.32
CABG-related major bleeding, TIMI criteria	446 (5.3)	476 (5.8)	0.94 (0.82-1.07)	0.32
Major or minor bleeding, PLATO criteria	1339 (16.1)	1215 (14.6)	1.11 (1.03-1.20)	0.008
Major or minor bleeding, TIMI criteria[c]	946 (11.4)	906 (10.9)	1.05 (0.96-1.55)	0.33

CABG = coronary artery bypass grafting; CI = confidence interval; n = number of patients; PLATO = a study of PLATelet inhibition and patient Outcomes; TIMI = Thrombolysis in Myocardial Infarction. [a] Data are shown for patients who received at least 1 dose of study drug for events occurring up to 7 days after permanent discontinuation of the study drug. The percentages for the primary and secondary safety endpoints are Kaplan-Meier estimates for the rate of the end point at 12 months. Patients could have more than 1 type of end point. [b] Hazard ratios are shown for all safety endpoints except bleeding requiring red cell transfusion for which odds ratio are shown. The p-values for odds ratios were calculated with the use of Fischer's exact test. [c] Major bleeding and major or minor bleeding according to TIMI criteria refer to nonadjudicated events analyzed with the use of a statistically programmed analysis in accordance with previously used definitions.

Other Safety Endpoints

- Premature discontinuation of study drug occurred in 23.4% and 21.5% of patients in the ticagrelor and clopidogrel groups, respectively (p=0.002). Of these early discontinuations, 7.4% of patients in the ticagrelor group compared to 6.0% of patients in the clopidogrel group withdrew because of AEs (p<0.001).

- Dyspnea was reported in 13.8% of ticagrelor-treated and 7.8% of clopidogrel-treated patients with 0.9% and 0.1% of patients, respectively, discontinuing study treatment as a result (p<0.001 for both comparisons).

- Neoplasms were reported in 1.4% and 1.7% of ticagrelor- and clopidogrel-treated patients, respectively (p=0.17).

- There were no statistical differences in the occurrence of bradycardia, pacemaker insertion, syncope, or heart block between treatment groups.

- Holter monitoring was performed in a subgroup of patients during the first week of therapy and at 30 days of therapy to evaluate the occurrences of ventricular pauses. The ticagrelor group had a higher incidence of ventricular pauses in the first week, but not at Day 30, when compared to the clopidogrel group. Pauses were rarely associated with symptoms. In the first week, ventricular pauses lasting ≥3 seconds occurred in 5.8% and 3.6% of patients receiving ticagrelor and clopidogrel, respectively (p=0.01). By Day 30, the incidence of ventricular pauses lasting ≥3 seconds was 2.1% in patients receiving ticagrelor and 1.7% in patients receiving clopidogrel (p=0.52).

- Laboratory test changes included greater increases in serum uric acid levels in the ticagrelor group compared to the clopidogrel group at 1 and 12 months of treatment (14%-15% in the ticagrelor group vs. 7% in the clopidogrel group; p<0.001 both time points). At 1 month after the end of treatment, there was no difference between treatment groups with regard to changes in uric acid levels (p=0.56). Ticagrelor-treated patients experienced a greater change in serum creatinine levels from baseline (10%-11%) at 1 and 12 months of therapy (p<0.001 for both time points) than clopidogrel-treated patients (8%-9%). The difference between groups was not statistically significant by 1 month after the end of treatment (+10% for both groups; p=0.59).

Mahaffey KW, Wojdyla DM, Carroll K, et al for the PLATO investigators. Ticagrelor compared with clopidogrel by geographic region in the platelet inhibition and patient outcomes (PLATO) trial. *Circulation.* 2011;124:544-554.

Mahaffey KW, Wojdyla DM, Carroll K, et al for the PLATO investigators. Data supplement. *Circulation.* 2011. Available at: http://circ.ahajournals.org/content/early/2011/06/27/CIRCULATIONAHA.111.047498/rel-suppl/38733e1ac2b68d61/suppl/DC1. Accessed July 20, 2011.

Study dates, study locations, inclusion and exclusion criteria, patients, endpoints: This study was an analysis of data from the PLATO trial. See the preceding text in this section for a description of PLATO.

Study objective: In the PLATO trial, results in the rest of the world (ROW) compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/nonUS comparison is statistically significant (p=0.009), and the same trend is present for both CV death and nonfatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and nonfatal MI components, however, supports the possibility that the finding is reliable.

Duke Clinical Research Institute (DCRI) conducted an independent analysis of potential explanations for the regional interaction observed in the PLATO study.

Study design: Baseline characteristics and patient management strategies were evaluated by an analysis of 31 prespecified subgroups and 6 postrandomization variables. Factors that were evaluated included ASA loading and maintenance doses, as well as other baseline and clinical management variables. The DCRI team reviewed the methodology that was used by AstraZeneca to rule out systematic errors in trial conduct. In addition, the possibility of the regional interaction occurring due to chance alone was investigated and could not be ruled out.

Results:

- The data for ticagrelor were consistent with the overall study population in all but 3 subgroups. The benefit of ticagrelor appeared to be attenuated in patients with body weight below the median for their sex (p=0.04 for the interaction); in patients not taking lipid-lowering drugs at randomization (p=0.04 for the interaction), and in patients enrolled from North America (p=0.045 for the interaction). In North America, ticagrelor did not result in a lower event rate compared to clopidogrel.
- Among the 37 multiple patient factors and concomitant therapies explored, investigators identified ASA maintenance dose as accounting for a substantial portion of the regional interaction. Results of the analyses by AstraZeneca using the median maintenance dose of ASA indicated that ASA maintenance dose could account for 80–100% of the observed regional interaction. The landmark approach using the ASA dose taken on Day 4 explained approximately 40% of the interaction effect. Figure 3-1 illustrates the time course of the primary efficacy outcome by treatment and daily maintenance ASA dose <300 mg and ≥300 mg. Figure 3-2 presents the adjusted HR for low versus high ASA dose by landmark dates and randomized treatment.
- Both analyses found that when given with low-dose ASA, ticagrelor achieved lower event rates for the primary efficacy endpoint compared to clopidogrel in the ROW and in the US. In an assessment of bleeding by region, no treatment-by-region interaction (p=0.9048) was observed for PLATO-defined major bleeding (US: 12.2% with ticagrelor vs. 11.9% with clopidogrel, p=0.7572; ROW: 11.5% with ticagrelor vs. 11.1% with clopidogrel, p=0.4696); therefore, the results were similar to those of the overall study.

FIGURE 3-1: Kaplan-Meier Estimated Event Rates.[a]

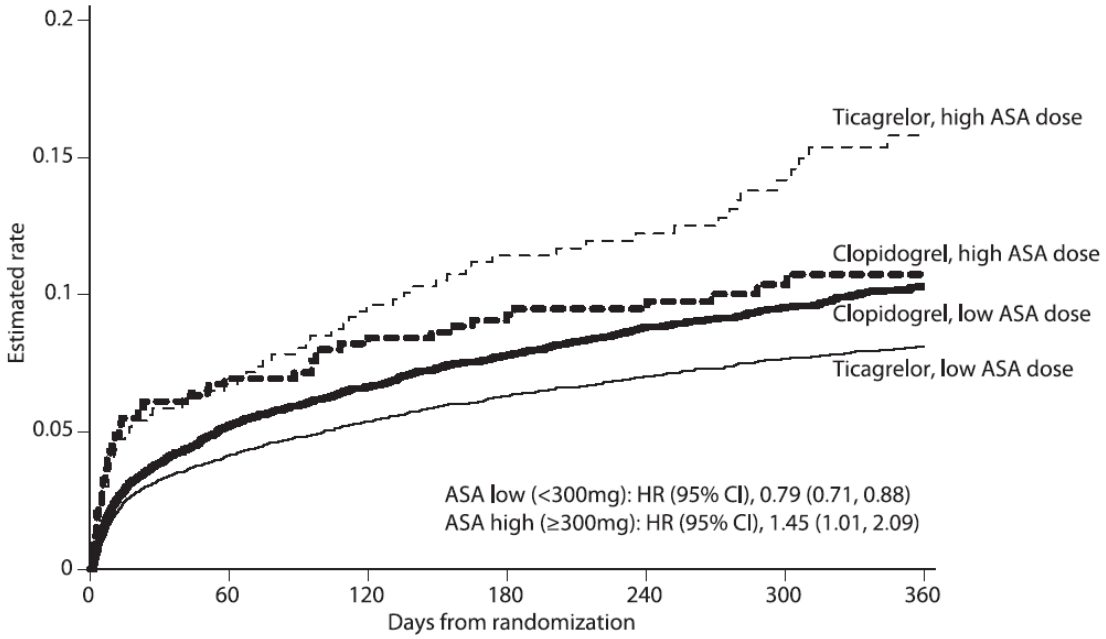
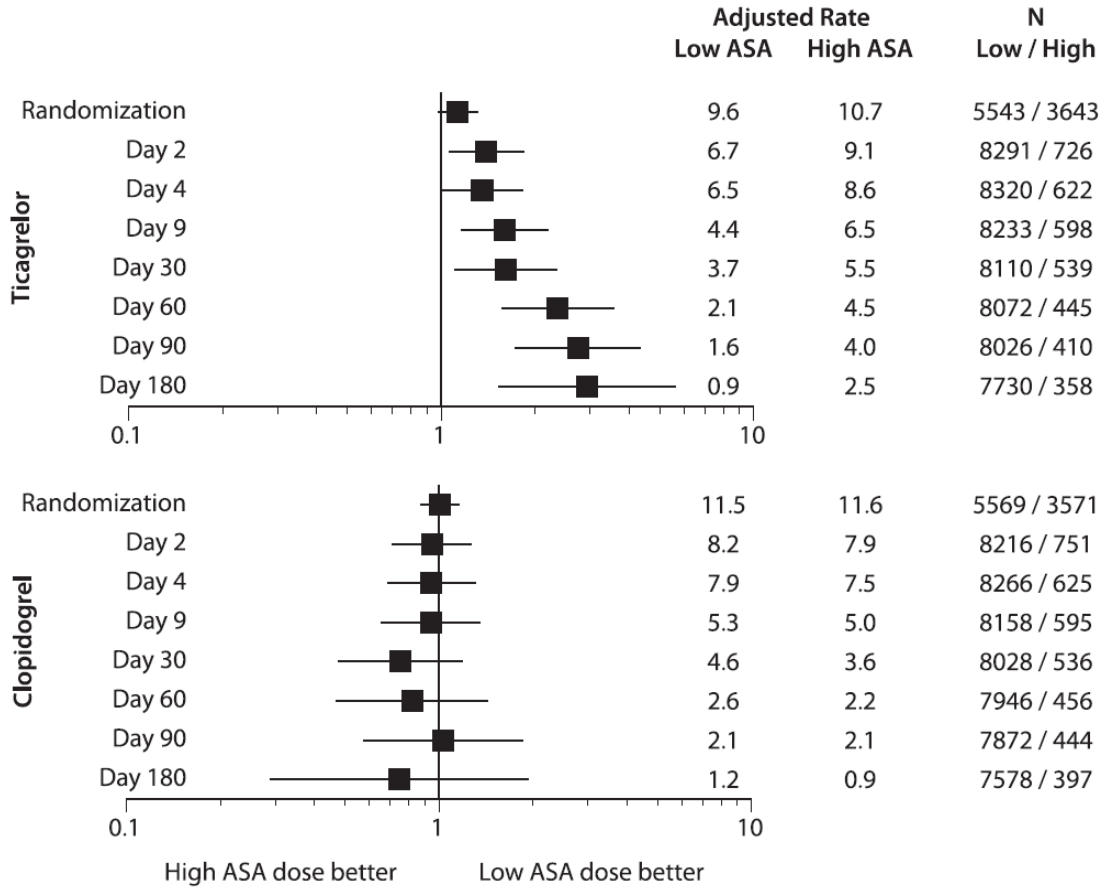


FIGURE 3-2: Landmark Technique.[a]



[a]Figures 3-1 and 3-2 are copyright-protected works. Unless you have the permission of the copyright owner, or a license from an appropriate authorized licensing body, you may not copy, store in any electronic medium or otherwise reproduce or resell any of the content, even for internal purposes, except as may be allowed by law.

James S, Roe M, Cannon CP, et al for the PLATO study group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for a noninvasive management: substudy from prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial [published online ahead of print]. *BMJ*. 2011. Available at: http://www.bmj.com/content/342/bmj.d3527.full.pdf?sid=be2340bd-42ec-4ae1-8e63-58e1b2f453c7. Accessed July 20, 2011.

Study dates, study locations, inclusion and exclusion criteria, treatment arms/dosing: All were identical to those for the overall PLATO trial and were presented in the preceding text of this section (Wallentin et al, 2009a; James et al, 2009).

Study objectives: To compare the efficacy and safety of ticagrelor versus clopidogrel in patients in the PLATO trial with a planned noninvasive treatment at randomization (James et al, 2010e)

Study design: Prespecified analysis of a prerandomized subgroup of patients from the PLATO trial with a planned noninvasive strategy at randomization.

Patients:

- 28% of patients (5216/18,624) in the PLATO trial[1] with a planned noninvasive strategy at randomization were included in this substudy.
- At randomization, the investigator entered their intent to manage the patient with an invasive or noninvasive strategy into the Interactive Voice Response System. These assignments were nonbinding but created statistically proper pre hoc subgroups for this analysis. After randomization, patients could undergo invasive procedures (angiography and revascularization) based on clinical need, regardless of initial assignment.
- After randomization, patients were eligible to receive angiography and/or revascularization based on clinical status despite original plan for noninvasive management.

Endpoints:

- The primary efficacy endpoint was the composite of CV death, MI, or stroke.
- The primary safety endpoint was PLATO-defined total major bleeding.

Follow-up: Patients were evaluated at 1, 3, 6, 9, and 12 months after hospital admission and 1 month following discontinuation of study treatment.

Patient Characteristics:

- Patients with a planned noninvasive management had different baseline characteristics versus those with a planned invasive strategy. Patients in the noninvasive cohort were older, more were women, and more had a history of heart disease versus patients in the invasive cohort.
- ACS type at final diagnosis differed between patients in the noninvasive cohort versus the invasive cohort. The majority of patients in the noninvasive cohort were diagnosed with either NSTEMI or UA at discharge.
- At the end of follow-up, 60.3% of patients in the noninvasive cohort were ultimately managed noninvasively.
- At the end of follow-up, 40% of patients (n=2040) in the noninvasive cohort had undergone revascularization with 72.6% (n=1514) having PCI only, 25.8% (n=559) having CABG only, and 1.6% (n=33) having both PCI and CABG.

- A comparison of patient demographics is presented in the following table.

TABLE 3-7: Patient Characteristics.[a] Adapted from Adapted from *BMJ*. 2011 [online ahead of print].

	Planned Noninvasive Management			Planned Invasive Management
	Ticagrelor (n=2601)	**Clopidogrel (n=2615)**	**Total (n=5216)**	**Total (n=13,408)**
Demographics				
Median (IQR) age, years	66 (57-73)	65 (57-73)	65 (57-73)	61 (53-69)[b]
Age, ≥75years	553 (21.3)	555 (21.2)	1108 (21.2)	1770 (13.2)
Women	961 (36.9)	945 (36.1)	1906 (36.5)	3382 (25.2)
CV Risk Factors				
Habitual smoker	654/2600 (25.2)	675/2614 (25.8)	1329/5214 (25.5)	5349/13,396 (39.9)
Hypertension	1868/2600 (71.8)	1893 (72.4)	3761/5215 (72.1)	8422/13,398 (62.9)
Dyslipidemia	1223/2600 (47.0)	1191 (45.5)	2414/5215 (46.3)	6275/13,397 (46.8)
DM	796/2600 (30.6)	757 (28.9)	1553/5215 (29.8)	3109/13,398 (23.2)
History				
Angina pectoris	1547/2600 (59.5)	1536 (58.7)	3083/5215 (59.1)	5275/13,398 (39.4)
MI	752/2600 (28.9)	793 (30.3)	1545/5215 (29.6)	2279/13,398 (17.0)
CHF	290/2600 (11.2)	324 (12.4)	614/5215 (11.8)	436/13,398 (3.3)
PCI	325/2600 (12.5)	335 (12.8)	660/5215 (12.7)	1832/13,397 (13.7)
CABG	175/2600 (6.7)	194 (7.4)	369/5215 (7.1)	737/13,398 (5.5)
TIA	101/2600 (3.9)	110 (4.2)	211/5215 (4.0)	288/13,398 (2.1)
Non-hemorrhagic stroke	144/2600 (5.5)	151/2614 (5.8)	295/5214 (5.7)	427/13,398 (3.2)
PAD	191/2600 (7.3)	210 (8.0)	401/5215 (7.7)	743/13,398 (5.5)
Chronic renal disease	131/2600 (5.0)	143 (5.5)	274/5215 (5.3)	511/13,398 (3.8)
Type of ACS at Discharge				
STEMI	218/2594 (8.4)	233/2608 (8.9)	451/5202 (8.7)	6575/13,380 (49.1)
NSTEMI	1441/2594 (55.6)	1469/2608 (56.3)	2910/5202 (55.9)	5045/13,380 (37.7)
UA or other	935/2594 (36.0)	906/2608 (34.7)	1841/5202 (35.4)	1760/13,380 (13.2)

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; IQR = interquartile range; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina. [a]Data are presented as n (%) unless otherwise noted; [b]n=13,406.

Results:

Efficacy

- In the planned noninvasive cohort, ticagrelor significantly reduced the incidence of the primary composite endpoint (CV death, MI, or stroke), all-cause mortality, and CV death versus clopidogrel.

- The rate of stroke did not differ significantly between treatment groups; however, numerically more hemorrhagic strokes occurred with ticagrelor.

- The benefit of ticagrelor versus clopidogrel was consistent in both patients managed invasively and those managed noninvasively with the HR for the noninvasive cohort being 0.85 (95% confidence interval [CI]: 0.85-1.00) and the HR for the invasive cohort being 0.84 (95% CI: 0.75-0.94); p-value for the interaction=0.89.

- Results for efficacy endpoints are provided in the following table.

TABLE 3-8: Occurrence of Efficacy Endpoints in Patients With a Planned Noninvasive Treatment.[a,b]
Adapted from *BMJ*. 2011 [online ahead of print].

	Ticagrelor (n=2601)	Clopidogrel (n=2615)	HR (95% CI)	p-value
Primary Endpoint				
CV death, MI (excluding silent), or stroke	295 (12.0)	346 (14.3)	0.85 (0.73-1.00)	0.045
Secondary Endpoints				
MI	176 (7.2)	187 (7.8)	0.94 (0.77-1.15)	0.555
CV death	132 (5.5)	173 (7.2)	0.76 (0.61-0.96)	0.019
All-cause mortality	147 (6.1)	195 (8.2)	0.75 (0.61-0.93)	0.010
Non-CV death	15 (0.6)	22 (1.0)	0.68 (0.35-1.31)	0.252
Stroke	50 (2.1)	37 (1.7)	1.35 (0.89-2.07)	0.162
Ischemic	37 (1.5)	32 (1.4)	NR	0.530
Hemorrhagic	11 (0.5)	4 (0.2)	NR	0.069
Unknown	5 (0.2)	1 (0.06)	NR	0.124
CV death, MI, stroke, composite ischemic events,[c] or other arterial events	460 (18.6)	492 (20.3)	0.94 (0.82-1.06)	0.309

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NR = not reported. [a]Values are Kaplan-Meier estimates at 360 days; [b]Data are presented as n (%) unless otherwise noted; [c]Severe recurrent cardiac ischemia, recurrent cardiac ischemia, and transitory ischemic attack.

Safety

- No statistically significant differences in the rate of PLATO-defined major bleeding were observed. Numerically more intracranial bleeding occurred with ticagrelor versus clopidogrel, but the difference was not significant.

- Results for safety endpoints are provided in the following table.

TABLE 3-9: Occurrence of Bleeding in Patients With a Planned Noninvasive Treatment.[a] Adapted from *BMJ*. 2011 [online ahead of print].

	Ticagrelor (n=2601)	Clopidogrel (n=2615)	HR (95% CI)	p-value
Primary Safety Endpoint				
Total major bleeding	272 (11.9)	238 (10.3)	1.17 (0.98-1.39)	0.079
Life-threatening or fatal bleeding	125 (5.5)	129 (5.6)	0.99 (0.77-1.26)	0.911
Intracranial bleeding	11 (0.5)	4 (0.2)	2.83 (0.90-8.90)	0.075
Other major bleeding	154 (6.8)	114 (4.9)	1.38 (1.09-1.76)	0.009
Secondary Safety Endpoint—Components of Major Bleeding Events				
Non-CABG-related	90 (4.0)	71 (3.1)	1.30 (0.95-1.77)	0.103
CABG-related	189 (8.3)	174 (7.5)	1.11 (0.90-1.36)	0.335
Coronary procedure-related	211 (9.2)	191 (8.2)	1.13 (0.93-1.37)	0.231
Noncoronary procedure-related	1 (0.04)	7 (0.4)	0.15 (0.02-1.19)	0.072
Secondary Safety Endpoint—Major or Minor Bleeding Events				
Total	378 (16.4)	332 (14.4)	1.17 (1.01-1.36)	0.0358
NonCABG-related	190 (8.3)	151 (6.7)	1.29 (1.04-1.60)	0.0182
CABG-related	202 (8.9)	196 (8.5)	1.05 (0.86-1.28)	0.6341
Coronary procedure-related	250 (10.8)	235 (10.0)	1.09 (0.91-1.30)	0.3657
Non-coronary procedure-related	11 (0.5)	16 (0.8)	0.70 (0.33-1.51)	0.3632
Other Safety Endpoints				
TIMI-defined cutoff point for major bleeding				
Total	181 (7.9)	164 (7.2)	1.13 (0.91-1.39)	0.270
NonCABG-related	61 (2.8)	47 (2.2)	1.33 (0.91-1.94)	0.142
CABG-related	124 (5.4)	122 (5.3)	1.03 (0.80-1.33)	0.799
Transfusion of blood products				
PRBCs	174 (7.6)	172 (7.2)	1.03 (0.83-1.27)	0.804
Platelets	30 (1.3)	27 (1.2)	1.13 (0.67-1.90)	0.645
Fresh frozen plasma	55 (2.4)	50 (2.2)	1.12 (0.76-1.64)	0.565

CABG = coronary artery bypass graft; CI = confidence interval; HR = hazard ratio; PRBCs = packed red blood cells; TIMI = Thrombolysis In Myocardial Infarction. [a]Kaplan-Meier estimates of n (%) at 12 months.

Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study. *Lancet.* 2010;375:283-293.

Study dates, study locations, study design, inclusion and exclusion criteria, treatment arms/dosing: All were identical to those for the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009).

Study objective: To compare ticagrelor to clopidogrel for the prevention of CV events in patients with ACS and a planned invasive strategy in the PLATO trial (Cannon et al, 2010).

Sample characteristics: A subgroup of 13,408 patients in the PLATO study had a planned invasive strategy and was included in the substudy.

Endpoints:

Primary Endpoints:

- Composite of death from vascular causes, MI, or stroke
- PLATO-defined total major bleeding

Secondary Endpoints:

- Composite of all-cause mortality, MI, or stroke
- Death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack, or other arterial thrombotic event
- Components of the primary endpoint
- All-cause mortality
- Stent thrombosis

Results:

- Of the 18,624 patients randomized in PLATO, 13,408 (72%) were specified by the investigator as having the intent for invasive treatment strategy at the time of randomization.
- Baseline characteristics of patients were similar between treatment groups.

TABLE 3-10: Select Baseline Characteristics at Randomization in Patients With Intent for Invasive Management. Adapted from *Lancet*. 2010;375:283-293.

Baseline Characteristics	Ticagrelor (n=6732)	Clopidogrel (n=6676)
Age, median (yrs)	61.0	61.0
Age ≥75 years	12.5%	13.9%
Women	25.2%	25.3%
Ethnic origin		
Caucasian	91.2%	90.7%
Black	1.3%	1.5%
Asian	6.1%	6.4%
Other	1.4%	1.4%
Cardiac history/risk		
Previous MI	17.1%	16.9%
Previous PCI	14.1%	13.3%
Previous CABG	5.3%	5.7%
Previous transient ischemic attack	2.2%	2.1%
Previous nonhemorrhagic stroke	3.1%	3.3%
Diabetes mellitus	22.7%	23.7%
Invasive procedures during initial hospitalization		
Coronary angiography	6511 (96.7%)	6476 (97.0%)
Primary PCI[a] for STEMI	2986 (44.4%)	2984 (44.7%)
Other PCI[b] before discharge for first event	2173 (32.3%)	2155 (32.3%)
PCI (total)	5159 (76.6%)	5139 (77.0%)
CABG before discharge	372 (5.5%)	410 (6.1%)

CABG = coronary artery bypass graft; CI = confidence interval; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction. [a] Any PCI during the first 24 h after randomization. [b] Any PCI after first 24 h following randomization in patients with STEMI, or any PCI in patients with NSTEMI.

- The percentage of patients diagnosed with STEMI, NSTEMI, UA, or other ACS was similar between treatment groups.
- The administration of ASA, unfractionated heparin, low-molecular-weight heparin, fondaparinux, bivalirudin, or GP IIb/IIIa inhibitors during the initial hospital admission was similar between treatment groups.
- Results for the primary and secondary efficacy endpoints are provided in the following tables.

TABLE 3-11: Efficacy Endpoints for Patients With Intent for Invasive Management. Adapted from *Lancet*. 2010;375:285.

Endpoints, n (%)	Ticagrelor (n=6732)	Clopidogrel (n=6676)	Hazard Ratio for Ticagrelor (95% CI)	p-value
Primary Endpoint				
CV death, MI,[a] and stroke	569 (9.0%)	668 (10.7%)	0.84 (0.75-0.94)	0.0025
Secondary Endpoints				
All-cause mortality, MI,[a] and stroke	595 (9.4%)	701 (11.2%)	0.84 (0.75-0.94)	0.0016
CV death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack, and other arterial thrombotic event	830 (13.1%)	964 (15.3%)	0.85 (0.77-0.93)	0.0005
MI[a]	328 (5.3%)	406 (6.6%)	0.80 (0.69-0.92)	0.0023
CV death	221 (3.4%)	269 (4.3%)	0.82 (0.68-0.98)	0.0250
Stroke	75 (1.2%)	69 (1.1%)	1.08 (0.78-1.50)	0.6460
Ischemic[b]	59 (0.9%)	59 (0.9%)	—	1.0000
Hemorrhagic[b]	12 (0.2%)	9 (0.1%)	—	0.6634
Unknown[b]	5 (0.07)	1 (0.01%)	—	0.2187
All-cause mortality	252 (3.9%)	311 (5.0%)	0.81 (0.68-0.95)	0.0103

CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention. [a] Silent MI were excluded. [b] Number (%) are shown; Fisher's exact test was used to calculate the p-values.

TABLE 3-12: Stent Thrombosis in Patients With Intent for Invasive Management. Adapted from *Lancet*. 2010;375:285.

Stent Thrombosis, n (%)	Ticagrelor (n=4949)	Clopidogrel (n=4928)	Hazard Ratio for Ticagrelor (95% CI)	p-value
Definite	62 (1.3%)	97 (2.0%)	0.64 (0.46-0.88)	0.0054
Drug-eluting stent	17 (1.3%)	25 (1.8%)	0.69 (0.37-1.27)	0.2304
Bare-metal stent	45 (1.4%)	72 (2.1%)	0.62 (0.43-0.90)	0.0115
Definite or probable	104 (2.2%)	142 (3.0%)	0.73 (0.57-0.94)	0.0142
Drug-eluting stent	32 (2.3%)	36 (2.5%)	0.90 (0.56-1.45)	0.6581
Bare-metal stent	72 (2.2%)	106 (3.1%)	0.67 (0.50-0.91)	0.0092
Total (definite, probable, or possible)	132 (2.8%)	179 (3.8%)	0.73 (0.59-0.92)	0.0068
Drug-eluting stent	41 (3.1%)	53 (3.8%)	0.78 (0.52-1.17)	0.2349
Bare-metal stent	91 (2.7%)	126 (3.8%)	0.71 (0.55-0.94)	0.0142

CI = confidence interval.

Safety

- 29.4% of patients withdrew from the study because of AEs. The rate of discontinuation was not different between the 2 treatment groups.
- The rate of PLATO-defined total major bleeding was not different in the ticagrelor and clopidogrel treatment groups.
- The rate of life-threatening or fatal bleeding or other major bleeding was not different in the ticagrelor and clopidogrel treatment groups.
- Dyspnea occurred more frequently in the ticagrelor group. Treatment was discontinued in 0.8% of patients in the ticagrelor group and 0.2% in the clopidogrel group because of this AE.
- Further information on safety results are provided in the following table.

TABLE 3-13: Safety Results for Patients With Intent for Invasive Management. Adapted from *Lancet*. 2010;375:283-293.

Adverse Event, n (%)	Ticagrelor (n=6651)	Clopidogrel (n=6585)	HR for Ticagrelor (95% CI)	p-value[a]
Primary endpoint				
PLATO-defined total major bleeding	689 (11.5%)	691 (11.6%)	0.99 (0.89-1.10)	0.8803
Life-threatening or fatal bleeding	366 (6.0%)	351 (5.9%)	1.04 (0.90-1.20)	0.6095
Intracranial bleeding	15 (0.3%)	11 (0.2%)	1.36 (0.63-2.97)	0.4364
Other major bleeding	340 (5.9%)	360 (6.2%)	0.94 (0.81-1.09)	0.4030
Major bleeding events				
Non-CABG-related	272 (4.7%)	235 (4.0%)	1.16 (0.97-1.38)	0.1040
CABG-related	430 (7.1%)	480 (8.0%)	0.89 (0.78-1.01)	0.0745
Coronary procedure related	521 (8.5%)	554 (9.2%)	0.93 (0.83-1.05)	0.2573
Non-coronary procedure related	26 (0.5%)	30 (0.6%)	0.87 (0.51-1.46)	0.5911
Major or minor bleeding events				
Total	961 (16.0%)	883 (14.7%)	1.09 (0.99-1.19)	0.0700
Non-CABG-related	523 (8.9%)	416 (7.1%)	1.26 (1.11-1.43)	0.0004
CABG-related	464 (7.7%)	516 (8.7%)	0.89 (0.79-1.01)	0.0710
Coronary procedure related	645 (10.5%)	652 (10.7%)	0.98 (0.88-1.10)	0.7768
Non-coronary procedure related	42 (0.7%)	50 (0.9%)	0.84 (0.56-1.26)	0.3998
Transfusion of packed RBCs or whole blood	531 (8.9%)	525 (8.7%)	1.01 (0.89-1.14)	0.9095
Transfusion of platelets	98 (1.6%)	114 (1.9%)	0.85 (0.65-1.12)	0.2506
TIMI-defined major bleeding, total	476 (7.9%)	474 (7.9%)	1.00 (0.88-1.14)	1.000
TIMI-defined minor bleeding, total	219 (3.8%)	220 (3.7%)	0.99 (0.82-1.19)	0.9218
TIMI-defined major or minor bleeding, total	675 (11.2%)	678 (11.3%)	0.99 (0.89-1.10)	0.8573
GUSTO-defined severe bleeding, all	185 (2.9%)	198 (3.2%)	0.91 (0.74-1.12)	0.3785
Dyspnea	924 (13.9%)	527 (8.0%)	—	<0.0001
Deaths from non-vascular causes	31 (0.5%)	42 (0.6%)	—	0.1979

CABG = coronary artery bypass graft; CI = confidence interval; GUSTO = global strategies for opening occluded coronary arteries; HR = hazard ratio; RBC = red blood cells; TIMI = Thrombolysis in Myocardial Infarction. [a]Calculated by use of a univariate Cox model.

Steg PG, James S, Harrington RA, et al for the PLATO study group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010;122:2131-2141.

Study dates, study locations, study design, treatment arms/dosing: All were identical to those for the overall PLATO trial and were presented in the preceding text of this section (Wallentin et al, 2009a; James et al, 2009).

Study objective: To evaluate the efficacy and safety of ticagrelor compared to clopidogrel in a subgroup of patients from the PLATO trial with ST-segment elevation ACS (STE-ACS) intended for reperfusion with primary PCI.

Inclusion and exclusion criteria: These criteria included those for the overall PLATO trial and the following:

- Persistent ST elevation ≥1 mV for ≥20 minutes (not known to be pre-existing or due to a co-existing disorder) in ≥2 contiguous leads and planned primary PCI within the first 24 hours of symptom onset or
- New or presumed new LBBB and planned primary PCI.
- Because of possible differences between admission and final diagnoses in patients with acute MI, sensitivity analyses were performed with different definitions of the STEMI, including those patients with STEMI as a discharge diagnosis.

Sample characteristics:

- Of the 18,624 randomized patients in the PLATO trial, 7544 patients presented with STE-ACS and an additional 886 patients had STEMI documented as a discharge diagnosis.
- The treatment groups were balanced with regards to baseline characteristics, initial treatments, and procedures.
  - Prior to randomization, 44% of patients received open-label clopidogrel.
  - In the first 24-hours (open-label and blinded), 35.6% of the patients received 600 mg of clopidogrel.
  - Median duration of treatment in this subgroup was 280 days with premature treatment discontinuation in 19.1% of the patients in the ticagrelor group and 18.4% in the clopidogrel group. Selected baseline characteristics are shown in the following table.

TABLE 3-14: Select Baseline Characteristics in Patients With ST-elevation ACS. Adapted from *Circulation.* 2010;122:2133.

Baseline Characteristics	Ticagrelor (n=3752)	Clopidogrel (n=3792)
Median age (years)	59	59
Female	24.2%	23.4%
CV risk factors		
Smoker	45.9%	44.3%
Hypertension	59.3%	58.3%
Dyslipidemia	39.0%	39.3%
Diabetes mellitus	19.1%	21.5%
History		
MI	13.3%	13.6%
Percutaneous coronary intervention	8.7%	8.0%
Coronary artery bypass graft	2.6%	2.6%
ECG findings at entry		
ST-segment elevation ≥1 mm	91.0%	89.9%
Left bundle branch block	9.0%	10.1%
Positive troponin I test (≥0.08 ng/mL) at study entry		
Yes	84.5%	85.5%
No	13.1%	11.8%

ACS = acute coronary syndrome; CV = cardiovascular; ECG = electrocardiogram; MI = myocardial infarction.

Endpoints: Endpoints were identical to those of the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009).

Results:

Efficacy

- Patients in the ticagrelor group had a 13% lower relative risk for the occurrence of a primary efficacy endpoint compared to clopidogrel-treated patients (9.4% vs. 10.8%, respectively; HR: 0.87; 95% CI: 0.75-1.01; p=0.07) (Steg et al, 2010).

- There was no significant interaction between the treatment effect and the presence or absence of ST-segment elevation/LBBB (interaction p-value: p=0.29).

- The effect of ticagrelor on the primary endpoint was consistent across the various predefined subgroups classified by prerandomization characteristics or postrandomization treatment use.

- For all regions other than North America, the HR for ticagrelor versus clopidogrel was <1 (interaction p-value: p =0.39).

- Using the sensitivity analysis, there was a similar effect on the primary endpoint for patients with STE-ACS at presentation, LBBB at presentation, and with a discharge diagnosis of STEMI.

- The incidence of several secondary efficacy endpoints was reduced in the ticagrelor group, including MI alone, total mortality, and definite stent thrombosis. The number of strokes was low for both groups, with a higher rate with ticagrelor (1.7% vs. 1.0%, p=0.02). Further details are provided in the following table.

TABLE 3-15: Major Efficacy Endpoints. Adapted from *Circulation.* 2010;122:2137.

Endpoints[a]	Ticagrelor (n=3752)	Clopidogrel (n=3792)	HR (95% CI)	p-value
Primary Endpoint, %				
CV, MI, stroke	9.4	10.8	0.87 (0.75-1.01)	0.07
Secondary Endpoints, %				
CV death and MI (excluding silent)	8.4	10.2	0.82 (0.71-0.96)	0.01
Total death, MI (excluding silent), stroke	9.8	11.3	0.87 (0.75-1.00)	0.05
CV death, MI (total), stroke, SRI, RI, TIA, arterial thrombotic events	13.3	15.0	0.87 (0.77-0.99)	0.03
MI (excluding MI)	4.7	5.8	0.80 (0.65-0.98)	0.03
CV death	4.5	5.5	0.83 (0.67-1.02)	0.07
Stroke	1.7	1.0	1.63 (1.07-2.48)	0.02
Non-hemorrhagic stroke	1.2	0.8	1.58 (0.97-2.56)	0.06
Hemorrhagic stroke	0.3	0.2	—[b]	—[b]
Stroke: unknown	0.1	0.0	—[b]	—[b]
Fatal stroke	0.37	0.16	2.36 (0.91-6.14)	0.08
All-cause mortality	5.0	6.1	0.82 (0.67-1.00)	0.05
Non-CV death	0.5	0.7	0.77 (0.40-1.48)	0.43
Stent Thrombosis Endpoints,[c] %				
Definite	1.6	2.4	0.66 (0.45-0.95)	0.03
Probable or definite	2.6	3.4	0.74 (0.55-1.00)	0.05
Possible, probable, or definite	3.3	4.3	0.75 (0.57-0.99)	0.04

CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; RI = recurrent cardiac ischemia; SRI = severe recurrent cardiac ischemia; TIA = transient ischemic attack. [a] The percentages are Kaplan-Meier estimates of the rate of the endpoint at 12 months. Patients could have had more than 1 type of endpoint; [b] HR and p-values are not reported when the total number of event <20; [c] Endpoints reported in patients that received at least 1 stent.

Safety:

- The rates of both PLATO-defined total major bleeding and TIMI-defined major bleeding were not different between groups (9.0% and 6.1%, respectively, in the ticagrelor group and 9.2% and 6.4%, respectively, in the clopidogrel group; p=NS for both comparisons).

- There was no difference between groups in fatal or life-threatening bleeding or in other major bleeding.

- The occurrence of the combination of nonprocedural major and minor bleeding was greater in the ticagrelor group than the clopidogrel group (5.1% vs. 3.7%, p=0.02). Further details are provided in the following table.

- Bleeding results were consistent in the sensitivity analysis adding the group of patients with a discharge diagnosis of STEMI.

TABLE 3-16: Major Safety Endpoints. Adapted from *Circulation.* 2010;121:2138.

Endpoints[a]	Ticagrelor (n=3719)	Clopidogrel (n=3752)	HR (95% CI)	p-value
PLATO definition, %				
Major	9.0	9.2	0.98 (0.83-1.14)	0.76
Life-threatening bleed	4.7	4.9	0.98 (0.79-1.22)	0.86
NonCABG-related major bleed	4.1	3.7	1.06 (0.84-1.35)	0.61
CABG-related major bleed[b]	5.1	5.8	0.90 (0.73-1.10)	0.30
Other procedure-related major bleed[c]	1.7	1.8	0.96 (0.68-1.36)	0.83
Non-procedure-related major bleed	2.6	2.0	1.19 (0.86-1.64)	0.30
Major and minor	13.1	12.3	1.05 (0.92-1.21)	0.43
Non-CABG-related major and minor bleed	7.7	6.5	1.16 (0.97-1.38)	0.11
CABG-related major and minor bleed	5.8	6.5	0.89 (0.73-1.09)	0.26
Other procedure-related major and minor bleed	3.2	3.1	1.05 (0.81-1.36)	0.72
Non-procedure-related major and minor bleed	5.1	3.7	1.31 (1.04-1.66)	0.02
Minor (only) bleed	4.9	3.8	1.26 (1.00-1.59)	0.05
TIMI definition, %[d]				
TIMI major bleed	6.1	6.4	0.96 (0.79-1.16)	0.66
Non-CABG-related TIMI major bleed	2.5	2.2	1.09 (0.80-1.48)	0.60
TIMI major and minor bleed	8.8	8.9	0.97 (0.83-1.14)	0.72
Non-CABG-related TIMI major and minor bleed	4.0	3.5	1.08 (0.85-1.38)	0.52
TIMI fatal/life threatening bleed	4.3	4.5	0.98 (0.78-1.23)	0.89
TIMI minor (only) bleed	3.0	2.8	1.04 (0.79-1.38)	0.77
Fatal Bleeds, %	0.2	0.1	--[e]	--[e]
Fatal non-intracranial	0.1	0.1	--[e]	--[e]
Fatal intracranial	0.1	0.1	--[e]	--[e]

CABG = coronary artery bypass grafting; HR = hazard ratio; TIMI = thrombolysis in myocardial infarction. [a]The percentages are Kaplan-Meier estimates of the rate of the endpoint at 12 months. Patients could have had more than 1 type of endpoint; [b]Percentages given are out of the total number of patients; [c]Procedural bleed includes coronary and noncoronary procedures; [d]TIMI bleeding rates were calculated, not adjudicated; [e]HR and p-values are not reported when the total number of event <20.

- Dyspnea occurred more frequently in the ticagrelor group compared with the clopidogrel group (12.6% vs. 8.4%; p<0.0001) but rarely required treatment discontinuation (0.5 vs. 0.1%; p=0.0004).

- The incidences of syncope, bradycardia, heart block, and the need for a pacemaker were not different between the groups.

Held C, Åsenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol*. 2011;57:672-684.

Study dates, study locations, inclusion and exclusion criteria: Identical to those for the overall PLATO trial and were presented in the preceding text of this section (Wallentin et al, 2009a; James et al, 2009).

Study objective: To evaluate the efficacy and safety of ticagrelor and clopidogrel in patients with ACS undergoing CABG surgery as a postrandomization strategy (Held et al, 2011).

Study design: This study was a retrospective analysis of a nonrandomized subgroup of patients from the PLATO trial who underwent CABG surgery and therefore provides exploratory information only. The PLATO trial was a randomized, double-blind, double-dummy, multinational study of 18,624 patients that compared the effects of ticagrelor plus aspirin with clopidogrel plus aspirin on the prevention of vascular events in patients presenting with ACS (Wallentin, 2009a). The statistical analysis was based on events occurring from the CABG procedure until the end of the study (Held, 2011).

Sample characteristics:

- In the PLATO trial, 1899 of 18,624 patients underwent CABG surgery postrandomization. This analysis included 1261 patients who underwent CABG with last intake of study drug ≤7 days prior to surgery.
- 94% of patients received aspirin prior to randomization.
- Open-label clopidogrel prior to randomization was used in 46.5% of ticagrelor-treated patients and 44.2% of clopidogrel-treated patients.
- Time to CABG after randomization did not differ between ticagrelor- and clopidogrel-treated patients (HR: 0.96; 95% CI: 0.87-1.05; p=0.36).
- Study drug was discontinued prior to surgery:
  - Within the first 2 days in 30.1% of ticagrelor-treated patients and 27.7% of clopidogrel-treated patients
  - Within 3-5 days in 43.8% of ticagrelor-treated patients and 37.9% of clopidogrel-treated patients
  - In >5 days in 26.1% of ticagrelor-treated patients and 34.5% of clopidogrel-treated patients
- Study drugs were restarted within 7 days postCABG in 57% of patients and within 14 days in 84% of patients, with no difference between the groups.
- Treatment groups were well balanced in regards to baseline characteristics, in-hospital treatments, and procedures.
- Baseline characteristics are presented in the following table.

TABLE 3-17: Select Baseline Characteristics in the Study Population at Randomization. Adapted from *J Am Coll Cardiol*. 2011;57:675.

Characteristic	Ticagrelor n=632	Clopidogrel n=629	p-value[a]
Age (years)[b]	64	64	0.3067
Age ≥75 years, n (%)	86 (13.6)	99 (15.7)	0.3013
Women	121 (19.1)	145 (23.1)	0.0976
BMI, women[b] kg/m^2	26.8	27.1	0.9528
BMI, men[b] kg/m^2	27.6	26.9	0.0450
CV risk factors, n (%)			
Smoker	208 (32.9)	185 (29.4)	0.1837
Hypertension	433 (68.5)	422 (67.1)	0.6297
Dyslipidemia	356 (56.3)	328 (52.1)	0.1419
Diabetes mellitus	193 (30.5)	207 (32.9)	0.3969
Other medical history, n (%)			
Angina pectoris	344 (54.4)	327 (52.0)	0.3975
MI	124 (19.6)	131 (20.8)	0.6238
PCI	58 (9.2)	73 (11.6)	0.1669
CABG	5 (0.8)	14 (2.2)	0.0395
Chronic renal disease	33 (5.2)	27 (4.3)	0.5087

BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention. [a]The p-values were calculated with Fisher's exact test (categorical variables) or Wilcoxon's rank sum test (continuous variables); [b]Values are median.

Treatment arms/dosing:

- Treatment with ticagrelor, clopidogrel, and ASA was the same as that described above for the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009).

- GP IIb/IIIa receptor antagonists and approved IV anticoagulants were allowed, but long-term treatment with low-molecular-weight heparin was not recommended.Oral anticoagulation was not permitted.

- It was recommended that ticagrelor/placebo-clopidogrel be withheld for 24-72 hours, and clopidogrel/placebo-ticagrelor be withheld for 5 days prior to CABG surgery. Study drugs were to be restarted immediately after surgery and prior to discharge.

Endpoints:

Primary Endpoints:

- Time from CABG to first occurrence of any event from the composite of death from vascular causes (CV death), MI, or stroke

- PLATO-defined major CABG-related bleeding

Secondary Endpoints:

- Components of the primary endpoint

- All-cause mortality

- CABG-related mortality

- Various bleeding analyses

Follow-up: Patients were evaluated at 1, 3, 6, 9, and 12 months after hospital admission and 1 month following discontinuation of study treatment (Wallentin et al, 2009a).

Results:

- Results for the primary and secondary efficacy endpoints are provided in the following table.

- CV death was reduced with ticagrelor (4.1%) compared to clopidogrel (7.9%), (48% RRR; p=0.0092).

- Total mortality in association with or after CABG was reduced with ticagrelor (4.7%) compared to clopidogrel (9.7%; 51% RRR; p=0.0018).

- A sensitivity analysis was performed using the total CABG population (n=1899), which included all CABG patients postrandomization, irrespective of timing of study drug intake. Results were consistent with the study population.

- PostCABG mortality results in relation to time from last study drug before surgery:
  - When the last intake of study drug before surgery was 1 day or less, there was no mortality difference between ticagrelor and clopidogrel.
  - If the last intake of study drug was 1-4 days before surgery:
    - Total mortality for ticagrelor vs. clopidogrel was 3.4% vs. 15.5%, respectively. (HR: 0.21; 95% CI: 0.10-0.42; p-interaction <0.01),
    - CV mortality for ticagrelor vs. clopidogrel was 3.1% vs. 11.8%, respectively. (HR: 0.25; 95% CI: 0.12-0.53; p-interaction <0.05).
  - When the last intake of study drug was >4 days before surgery, there was no mortality difference between ticagrelor and clopidogrel.

- There was no significant treatment by subgroup interaction for the outcomes of the primary efficacy composite, total mortality, or CV mortality for the following subgroups:
  - Open-label clopidogrel before randomization; hypertension; diabetes mellitus; smoking; dyslipidemia; age >75 years or age <75 years; weight >60 kg or <60 kg or >80 kg or <80 kg.

TABLE 3-18: Outcome After CABG Surgery in the Study Population. Adapted from *J Am Coll Cardiol*. 2011;57:678.

Endpoints	Ticagrelor[a] n=629 n(%)	Clopidogrel[a] n=629 n(%)	HR (95% CI)	p-value[b]
Primary Endpoint				
CV death/MI/ stroke	66 (10.6)	79 (13.1)	0.84 (0.60-1.16)	0.2862
Secondary Endpoints				
MI, excluding silent	37 (6.0)	35 (5.7)	1.06 (0.66-1.68)	0.8193
All-cause mortality	29 (4.7)	58 (9.7)	0.49 (0.32-0.77)	0.0018
CV death	25 (4.1)	47 (7.9)	0.52 (0.32-0.85)	0.0092
Non-CV death	4 (0.7)	11 (2.0)	0.35 (0.11-1.11)	0.0748
Stroke	13 (2.1)	11 (2.1)	1.17 (0.53-2.62)	0.6967
Hemorrhagic stroke	0 (0.0)	1 (0.2)		
Nonhemorrhagic/unknown stroke	13 (2.1)	10 (1.9)	1.29 (0.57-2.95)	0.5430

CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction. [a]Kaplan Meier estimate of the rate of the endpoint at 12 months postCABG; [b]p-values were calculated by means of Cox regression analysis.

Safety:

- Key safety results are provided in the following table.

- There was no significant difference in CABG-related major bleeding for ticagrelor compared to clopidogrel; event rates were 81.3% vs. 80.1%, respectively (HR: 1.01; 95% CI: 0.90-1.15; p=0.84).

- The occurrence of fatal bleeding was not different between groups (0.8% for ticagrelor and 1.0% for clopidogrel; p=0.7730).

- There were 2 intracranial bleeds, 1 in each treatment group.

- With respect to time from last intake of study drug before surgery, there was no difference in PLATO-defined major/fatal/life-threatening CABG-related bleeding between ticagrelor and clopidogrel, even when the drug was stopped 1 day before surgery; p-interaction 0.76.

- There were no significant differences in other bleeding parameters included in this analysis.

TABLE 3-19: Selected Bleeding Complications During and After CABG. Adapted from *J Am Coll Cardiol*.2011;57:680.

Adverse Event	Ticagrelor[a] n=632 n (%)	Clopidogrel[a] n=629 n (%)	OR / HR (95% CI)	p-value[b]
Primary Safety Endpoint				
Major CABG-related bleeding[c]	513 (81.2)	504 (80.1)	1.07 (0.80-1.43)	0.6691
Other Bleeding Analyses				
CABG-related life-threatening/fatal[c]	276 (43.7)	268 (42.6)	1.04 (0.83-1.31)	0.7330
Fatal CABG bleeds[c]	5 (0.8)	6 (1.0)	0.83 (0.20-3.28)	0.7730
CABG-related intracranial bleeding[c]	0 (0.0)	0 (0.0)		
All intracranial bleeding postCABG	1 (0.2)	1 (0.2)	1.01 (0.06-16.09)	0.9967
CABG TIMI, all major[c]	375 (59.3)	362 (57.6)	1.08 (0.85-1.36)	0.5300
CABG TIMI, all minor[c]	133 (21.0)	136 (21.6)	0.97 (0.73-1.28)	0.8367
CABG-related GUSTO severe bleed[c]	67 (10.6)	77 (12.2)	0.85 (0.59-1.22)	0.3768

CABG = coronary artery bypass graft; CI = confidence interval; GUSTO = Global Strategies for Opening Occluded Coronary Arteries.; HR = hazard ratio; OR = odds ratio; TIMI = Thrombolysis In Myocardial Infarction; [a]For time-to-event outcomes, percent (%) is the Kaplan-Meier estimate of the rate of the endpoint at 12 months postCABG; [b]p-values are from Cox regression analysis (time-to-event outcomes) or Fisher's exact test (binary outcomes); [c]Binary outcome with OR.

Wallentin L, James S, Storey RF, et al, for the PLATO investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet.* 2010;376:1320-1328.

Study dates, study locations, inclusion and exclusion criteria: Dates and inclusion and exclusion criteria were the same as those used in the PLATO study (Wallentin et al, 2009a; James et al, 2009). Participation in the PLATO genetic substudy was voluntary for patients and sites (Wallentin et al, 2010).

Study objective: To investigate the role of CYP2C19 and ABCB1 polymorphisms on the efficacy and safety outcomes of the PLATO study

Study design: PLATO was a randomized, multicenter, double-blind, randomized study that compared ticagrelor to clopidogrel for the prevention of major CV events in patients with ACS treated with ASA.

Treatment arms/dosing:

- Treatment was the same as that in the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009). Patients were randomized within 24 hours of their ACS event to either
  - Ticagrelor: 180 mg LD followed by 90 mg twice daily or
  - Clopidogrel: 300 mg LD followed by 75 mg once daily
- Treatment lasted 12 months. In the ticagrelor arm, patients undergoing PCI received an additional 90-mg dose if the procedure was more than 24 hours after randomization. In the clopidogrel arm, patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.
- A single blood sample from 10,285 patients was obtained as close to randomization as possible, and genotyping was performed for the following alleles (Wallentin et al, 2010):
  - CYP2C19 LOF alleles *2, *3, *4, *5, *6, *7, *8
  - CYP2C19 GOF allele *17
  - ABCB1 single nucleotide polymorphism 3435C→T
- Comparisons of ticagrelor versus clopidogrel, stratified by genotype group, for the following outcomes:
  - primary efficacy composite of CV death, MI, or stroke
  - composite of CV death or MI
  - stent thrombosis
  - PLATO total major bleeding
  - PLATO non-CABG–related total major bleeding
  - PLATO CABG-related total major bleeding
  - composite of CV death, MI, stroke, and PLATO non-CABG–related major or PLATO CABG-related major fatal/life-threatening bleeding

Results:

- Baseline patient characteristics were similar between groups. In both groups of the genetic cohort, a majority (98%) of patients were Caucasian. Predicted phenotypes and allele frequencies were well balanced between the treatment groups.
- A data-driven statistical approach was used, with a guided decision to choose the most appropriate CYP2C19 genotype groupings for each composite endpoint within each treatment arm. An overall assessment of any effect of GOF alleles was followed by an ordered assessment of various logical groupings of CYP2C19 phenotypes.
- Comparisons of efficacy outcomes were based on the presence or absence of any CYP2C19 LOF allele.
- Groups identified for between-arm comparisons of bleeding endpoints were patients with GOF alleles, patients carrying LOF but no GOF CYP2C19 alleles, and patients with no LOF or GOF CYP2C19 alleles.

TABLE 3-20: Predicted CYP2C19 and ABCB1 Phenotypes. Adapted from *Lancet*. 2010;376:1322.

	Ticagrelor n=5137	Clopidogrel N=5148
CYP2C19 Predicted Phenotype, n (%)		
Extensive (*1/*1)	1849 (36)	1862 (36)
Intermediate (*1/*2-*8)	894 (17)	935 (18)
Poor (*2-*8 /*2-*8)	121 (2)	125 (2)
Poor or rapid heterozygote (*2-*8/*17)	369 (7)	328 (6)
Rapid heterozygote (*1/*17)	1437 (28)	1386 (27)
Ultra rapid (*17/*17)	268 (5)	268 (5)
Missing	199 (4)	244 (5)
ABCB1 Predicted Phenotype, n (%)		
High expression (C/C)	1167 (23)	1195 (23)
Intermediate expression (C/T)	2570 (50)	2518 (49)
Low expression (T/T)	1349 (26)	1386 (27)
Missing	51 (1)	49 (1)

CYP = cytochrome $P_{450.}$

CYP2C19 Genotype

- Outcomes in patients with CYP2C19 genotype are presented in the table below.

- A fewer number of events from the primary efficacy endpoint were seen with ticagrelor than clopidogrel in patients with any CYP2C19 LOF allele (HR: 0.77; 95% CI: 0.60-0.99; p=0.0380). A similar trend was also observed in patients without CYP2C19 LOF allele (HR: 0.86; 95% CI: 0.74-1.01; p=0.0608; p-value interaction=0.46). In the ticagrelor group, the rate of the primary efficacy endpoint was similar in patients with (8.6% per year) or without (8.8% per year) any LOF allele during the entire treatment period.

- A comparison of ticagrelor versus clopidogrel at 30 days showed numerically fewer composite events with ticagrelor (4.1%) than clopidogrel (5.7% [HR: 0.73; 95% CI: 0.52-1.03; p=0.078]) in patients with any LOF allele but similar results between treatment groups in patients without any LOF allele (3.8% in both groups).
- In the genotype subgroups (patients with any GOF allele, with LOF and no GOF alleles, and with no GOF or LOF alleles), results for PLATO-defined major bleeding were consistent with results for the overall PLATO population.

- Within the clopidogrel group, patients with any GOF allele had higher rates of PLATO-defined major bleeding (11.9% per year) compared to those without GOF or LOF alleles (9.5% per year, p=0.022).

- Regardless of CYP2C19 genotype group, there was no significant interaction between treatment groups and genotype groups in regards to major bleeding of any type.

ABCB1 Genotype

- Results for efficacy and bleeding endpoints in patients with low, intermediate, or high expression of the ABCB1 genotype were consistent with results in the overall PLATO population (table below).

Combined CYP2C19 and ABCB1 Genotypes

- In a post hoc analysis with a combination of data for CYP2C19 and ABCB1 polymorphisms, the event rate for ticagrelor-treated patients with any LOF CYP2C19 allele or ABCB1 high-expression allele (n=2253) was 8.6% per year, and the event rate for clopidogrel-treated patients in the same combined genotype group (n=2248) was 11.2% per year (HR: 0.75; 95% CI: 0.62-0.91; p=0.004).

- This genetic grouping did not have a significant interaction with the overall effects of ticagrelor versus clopidogrel (p=0.13).

TABLE 3-21: Selected Outcomes in Relation to CYP2C19 and ABCB1 Genotypes. Adapted from *Lancet*. 2010;376:1323.

	Ticagrelor 90 mg BID			Clopidogrel 75 mg QD					
	n	Patients With Events n (%)	KM (%)	n	Patients With Events n (%)	KM (%)	HR (95% CI)	p-value	p-value interaction[a]
CYP2C19 Genotype									
CV Death, MI, Stroke									
Any CYP2C19 LOF allele	1384	115 (8.3)	8.6	1388	149 (10.7)	11.2	0.77 (0.60-0.99)	0.0380	0.46
No CYP2C19 LOF allele	3554	296 (8.3)	8.8	3516	332 (9.4)	10.0	0.86 (0.74-1.01)	0.0608	
Major Bleeding/LOF									
Any CYP2C19 LOF allele	1380	149 (10.8)	11.8	1380	143 (10.4)	11.3	1.04 (0.82-1.30)	0.77	0.60
No CYP2C19 LOF allele	3547	331 (9.3)	10.3	3506	340 (9.7)	10.6	0.96 (0.83-1.12)	0.61	
Major Bleeding/GOF									
No CYP2C19 LOF, or GOF allele	1846	176 (9.5)	10.5	1856	161 (8.7)	9.5	1.12 (0.90-1.38)	0.31	0.19
Any CYP2C19 LOF, no GOF allele	1011	108 (10.7)	11.6	1053	108 (10.3)	11.1	1.03 (0.79-1.34)	0.84	
Any CYP2C19 GOF allele	2070	196 (9.5)	11.5	1977	214 (10.8)	11.9	0.86 (0.71-1.05)	0.13	
ABCB1 Genotype									
CV Death, MI, Stroke									
Low expression	1349	122 (9.0)	9.5	1386	137 (9.9)	10.5	0.90 (0.70-1.15)	0.40	0.39
Intermediate expression	2570	208 (8.1)	8.5	2518	233 (9.3)	9.8	0.86 (0.71-1.03)	0.11	
High expression	1167	98 (8.4)	8.8	1195	138 (11.5)	11.9	0.71 (0.55-0.92)	0.0104	
Major Bleeding									
Low expression	1345	132 (9.8)	10.9	1382	137 (9.9)	10.9	0.97 (0.76-1.23)	0.77	0.80
Intermediate expression	2567	240 (9.3)	10.3	2508	245 (9.8)	10.6	0.96 (0.80-1.15)	0.66	
High expression	1164	121 (10.4)	11.5	1188	116 (9.8)	10.8	1.06 (0.83-1.37)	0.63	

CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; CYP = cytochrome p_{450}; GOF = gain of function; HR = hazard ratio; KM = Kaplan-Meier; LOF = loss of function; MI = myocardial infarction; NR = not reported. [a]interaction p-value indicates the significance of the genotype group's effect on the results of treatment group comparisons.

James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. *Circulation.* 2010d;122:1056-1067.

Study dates: Enrollment for PLATO occurred between October 2006 and July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study locations: 862 centers in 43 countries, including the United States (Wallentin et al, 2009a; Wallentin et al, 2009b, supplementary appendix).

Study objective: To compare the main efficacy and bleeding outcomes of ticagrelor with those of clopidogrel in relation to renal function of patients in the PLATO trial (James et al, 2010d).

Study design:
- PLATO was a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared ticagrelor to clopidogrel for the prevention of CV events in 18,624 patients with ACS (Wallentin et al, 2009a; James et al, 2009).

- CrCL was calculated with the Cockroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) formula.

Inclusion/exclusion criteria:

Key inclusion criteria:
- Age ≥18 years

- Hospitalization with documented evidence of ACS (UA, NSTEMI, or STEMI) within 24 hours of randomization

Key exclusion criterion: End-stage renal failure that required dialysis

Treatment arms/dosing:
- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel:
  - Ticagrelor 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
  - Clopidogrel 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients also received ASA once daily unless intolerant.

Primary endpoints:
- The primary efficacy endpoint was the time to first occurrence of the composite of CV death, MI, or stroke.

- The primary safety endpoint was time to first occurrence of PLATO-defined major bleeding event.

Results:
- Serum creatinine (SCr) levels were available in 15,202 (81.9%) patients in the PLATO trial; median CrCL in these patients was 80.3 mL/min and 21% of these patients had CKD (defined as CrCL <60 mL/min) (James et al, 2010d).

- As seen in the following table, patients with CKD had more high-risk characteristics than patients with normal renal function. Within the CKD subgroup, baseline characteristics were balanced between treatment arms.

TABLE 3-22: Baseline Characteristics by Renal Function Using Cockroft-Gault Estimation. Adapted from *Circulation*. 2010d;122:1057.

Patient Characteristic	<60 mL/min (n=3237)	≥60 mL/min (n=11965)	p-value
Median age, years	74	60	<0.0001
Age ≥75 years, n (%)	1498 (46.3)	843 (7.1)	<0.0001
Female gender, n (%)	1289 (39.8)	3042 (25.4)	<0.0001
Median body weight, kg (quartiles)	72 (64-82)	81 (72-91)	<0.0001
Concomitant disease, n (%)			
Hypertension	2517 (77.8)	7392 (61.8)	<0.0001
Dyslipidemia	1548 (47.8)	5477 (45.8)	0.0388
Diabetes mellitus	1068 (33.0)	2763 (23.1)	<0.0001
History, n (%)			
Angina pectoris	1798 (55.6)	5097 (42.6)	<0.0001
MI	916 (28.3)	2200 (18.4)	<0.0001
CHF	406 (12.5)	449 (3.8)	<0.0001
PCI	510 (15.8)	1494 (12.5)	<0.0001
CABG	297 (9.2)	589 (4.9)	<0.0001
TIA	129 (4.0)	267 (2.2)	<0.0001
Nonhemorrhagic stroke	213 (6.6)	374 (3.1)	<0.0001
Peripheral arterial disease	314 (9.7)	634 (5.3)	<0.0001
Chronic renal disease	462 (14.3)	173 (1.5)	<0.0001
Biomarkers			
Creatinine (n=15502), µmol/L	115 (97-133)	80 (71-88)	<0.0001
Glucose (n=15192), mmol/L	7.2 (5.8-9.4)	6.8 (5.7-8.7)	<0.0001
Hemoglobin A_{1c} (n=14874), %	6.1 (5.7-6.9)	6.0 (5.6-6.5)	<0.0001
Hemoglobin (n=14609), mg/L	132 (120-144)	141 (131-150)	<0.0001
NT-proBNP (n=14428), ng/L	174 (54-565)	45 (16-131)	<0.0001
Troponin I (n=14923), µg/L	2.1 (0.2-13.1)	2.1 (0.2-11.7)	0.5781

CABG = coronary artery bypass graft; CHF = congestive heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCI = percutaneous coronary infusion; TIA = transient ischemic attack.

Efficacy Results:

- In the overall study population, 9.8% of ticagrelor-treated patients versus 11.7% of clopidogrel-treated patients experienced an event from the composite primary endpoint (HR: 0.84; 95% CI: 0.77-0.92; p<0.001) at 12 months.

- Baseline CrCL was a strong predictor of ischemic and bleeding endpoints. For every decrease in CrCL of 5 mL/min per 1.73 m^2 body surface area, a significant relative increase (p<0.001) was seen in the risk of the primary composite endpoint by 12%, total mortality by 19%, MI by 8%, stroke by 11%, and major bleeding by 4%.

- In patients with CKD, ticagrelor was associated with greater risk reduction than clopidogrel in the primary composite endpoint (RRR: 23%) and total mortality (RRR: 28%). The number needed to treat to prevent an additional event in patients with CKD was 21 (95% CI: 13-56) for the primary composite endpoint and 25 (95% CI: 16-63) for total mortality.

TABLE 3-23: Efficacy Outcomes in Patients With CKD or Normal Renal Function Using Cockcroft-Gault Estimation. Adapted from *Circulation*. 2010d;122:1059.

CrCL, mL/min	N	Overall		Ticagrelor		Clopidogrel		HR[a] (95% CI)	p-value for interaction
		n	%/year[a]	n	%/year[a]	n	%/year[a]		
Primary Composite Endpoint (CV death, MI, or Stroke)									
Overall	15,202	1538	10.8	703	9.8	835	11.7	0.84 (0.76-0.93)	0.13
<60	3237	591	19.7	252	17.3	339	22.0	0.77 (0.65-0.90)	
≥60	11,965	947	8.4	451	7.9	496	8.9	0.90 (0.79-1.02)	
All-cause Death									
Overall	15,202	728	5.2	321	4.5	407	5.8	0.79 (0.68-0.92)	0.16
<60	3237	353	12.1	144	10.0	209	14.0	0.72 (0.58-0.89)	
≥60	11,965	375	3.3	177	3.1	198	3.6	0.89 (0.73-1.09)	

CI = confidence interval; CKD = chronic kidney disease; CrCL = creatinine clearance; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; N = number of randomized patients; n = number of patients with 1 or more event. [a] Kaplan-Meier estimate at 360 days with HR and 95% CI.

- The group of patients who had CrCL <30 mL/min (n=214) had similar efficacy results.
  - Primary composite endpoint: 28.9% for ticagrelor (n=27) and 39.0% for clopidogrel (n=39; HR: 0.77, 95% CI: 0.49-1.30)
  - Total mortality: 23.4% for ticagrelor (n=21) and 29.6% for clopidogrel (n=29; HR: 0.77; 95% CI: 0.47-1.44)

- The primary composite endpoint and total mortality were reduced consistently with ticagrelor versus clopidogrel regardless of the CrCL cutoff value for CKD. Decreasing cutoff values of CrCL from 100 to 30 mL/min resulted in progressively decreasing point estimates of the HR.

- Using the MDRD formula to estimate renal function, 2562 patients were identified as having CKD. In this group, the ARR of the primary composite endpoint with ticagrelor versus clopidogrel was 6.0 % (RRR: 29%). Additional results are presented in the following table.

TABLE 3-24: Outcomes in Patients With CKD or Normal Renal Function Using MDRD Estimation. Adapted from *Circulation*. 2010d;122:1063.

CrCL, mL/min	N	Overall		Ticagrelor		Clopidogrel		HR (95% CI)	p-value for interaction
		n	%/year	n	%/year	n	%/year		
Primary Composite Endpoint (CV death, MI, or stroke)									
Overall	15,202	1538	10.8	703	9.8	835	11.7	0.84 (0.76-0.93)	0.03
<60	2562	457	19.4	189	16.4	268	22.4	0.71 (0.59-0.86)	
≥60	12,640	1081	9.1	514	8.5	567	9.6	0.90 (0.80-1.02)	
All Cause Death									
Overall	15,202	728	5.2	321	4.5	407	5.8	0.79 (0.68-0.92)	0.02
<60	2562	282	12.3	109	9.6	173	14.9	0.64 (0.50-0.81)	
≥60	12,640	446	3.8	212	3.5	234	4.0	0.91 (0.75-1.09)	
PLATO-defined Major Bleeding									
Overall	15,202	1518	11.1	781	11.5	737	10.7	1.07 (0.97-1.19)	0.98
<60	2562	319	14.3	161	14.5	158	14.2	1.08 (0.87-1.34)	
≥60	12,640	1199	10.5	620	10.9	579	10.1	1.08 (0.96-1.20)	

CI = confidence interval; CV = cardiovascular; CrCL = creatinine clearance; HR = hazard ratio; MI = myocardial infarction; N = number of randomized patients; n = number of patients with 1 or more event.

Safety Results:

- The risk of bleeding was increased in patients with CKD (see the following table).
- The incidence of PLATO-defined major bleeding was not significantly different between treatment groups in patients with normal renal function or in patients with CKD (using either Cockcroft-Gault equation or MDRD formula).
- The incidence of non-CABG major bleeding and intracranial bleeding was numerically higher with ticagrelor while the incidence of fatal bleeding was numerically higher with clopidogrel.
- The incidence of dyspnea was significantly greater with ticagrelor in patients with CKD and in patients with normal renal function.
- The occurrence of ventricular pauses ≥3 seconds at 1 week or at 30 days was not significantly different between treatment groups.
- Patients with normal renal function had a higher relative increase in SCr compared to patients with CKD. SCr from baseline to 12 months was significantly higher with ticagrelor compared to clopidogrel, but was similar between groups 1 month after the end of treatment.

TABLE 3-25: Safety Outcomes in Patients With CKD or Normal Renal Function Using Cockcroft-Gault Estimation. Adapted from *Circulation*. 2010d;122:1059.

CrCL, mL/min	N	Overall		Ticagrelor		Clopidogrel		HR[a] (95% CI)	p-value for interaction
		n	%/year[a]	N	%/year[a]	n	%/year[a]		
PLATO-defined Major Bleeding									
Overall	15,202	1518	11.1	781	11.5	737	10.7	1.07 (0.97-1.19)	
<60	3237	412	14.7	206	15.1	206	14.3	1.07 (0.88-1.30)	0.92
≥60	11,965	1106	10.2	575	10.6	531	9.8	1.08 (0.96-1.22)	
PLATO-defined Major or Minor Bleeding									
Overall	15,202	2074	15.2	1092	16.0	982	14.3	1.13 (1.04-1.23)	
<60	3237	571	20.2	300	22.0	271	18.6	1.19 (1.01-1.40)	0.54
≥60	11,965	1503	13.9	792	14.6	711	13.2	1.12 (1.01-1.24)	
PLATO-defined Non-CABG Major Bleeding									
Overall	15,202	536	4.0	293	4.4	243	3.6	1.22 (1.03-1.45)	
<60	3237	208	7.7	113	8.5	95	7.3	1.28 (0.97-1.68)	0.77
≥60	11,965	328	3.1	180	3.4	148	2.8	1.22 (0.98-1.51)	
PLATO-defined Fatal Major Bleeding									
Overall	15,202	36	0.29	19	0.30	17	0.28	1.13 (0.59-2.18)	
<60	3237	13	0.56	4	0.34	9	0.77	0.48 (0.15-1.54)	0.06
≥60	11,965	23	0.22	15	0.29	8	0.16	1.87 (0.79-4.41)	
TIMI Major or Minor Bleeding									
Overall	15,202	1487	10.9	768	11.3	719	10.5	1.08 (0.98-1.23)	
<60	3237	395	14.1	198	14.5	197	13.7	1.08 (0.88-1.31)	0.91
≥60	11,965	1092	10.1	570	10.5	522	9.6	1.09 (0.97-1.23)	
Non-CABG Major TIMI Bleeding									
Overall	15,202	323	2.4	179	2.7	144	2.2	1.26 (1.01-1.57)	
<60	3237	114	4.4	62	4.8	52	3.9	1.28 (0.88-1.85)	0.98
≥60	11,965	209	2.0	117	2.2	92	1.7	1.27 (0.97-1.67)	
Intracranial Bleeding									
Overall	15,202	35	0.28	22	0.35	13	0.21	1.72 (0.87-3.42)	
<60	3237	8	0.35	5	0.43	3	0.27	1.79 (0.43-7.51)	0.96
≥60	11,965	27	0.26	17	0.33	10	0.19	1.71 (0.78-3.74)	
Dyspnea									
Overall	15,202	1621	11.4	1034	14.4	587	8.3	1.84 (1.66-2.04)	
<60	3237	504	13.9	236	16.4	166	11.5	1.54 (1.27-1.88)	0.04
≥60	11,965	1219	10.7	798	13.9	421	7.5	1.96 (1.74-2.21)	
Ventricular Pauses ≥3 Seconds During First Week									
Overall	2356	107	4.5	63	5.3	44[b]	3.8[b]	1.44 (0.97-2.14)	
<60	480	24	5.0	13	5.4	11[b]	4.6[b]	1.16 (0.51-2.52)	0.56
≥60	1876	83	4.4	50	5.3	33[b]	3.5[b]	1.53 (0.98-2.40)	

CABG = coronary artery bypass graft; CI = confidence interval; CKD = chronic kidney disease; CrCL = creatinine clearance; HR = hazard ratio; N = number of randomized patients; n = number of patients with 1 or more event; PLATO = a study of PLATelet inhibition and patient Outcomes; TIMI = Thrombolysis in Myocardial Infarction. [a] Kaplan-Meier estimate at 360 days with HR and 95% CI; [b] Number of events with odds ratio and 95% CI.

Husted S, James S, Becker R, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and Patient Outcomes (PLATO) Trial [abstract and poster]. Presented at: 60th Annual Scientific Session of the American College of Cardiology; April 2-5, 2011; New Orleans, LA. *J Am Coll Cardiol*. 2011; 57(14 suppl 1):E1099. Abs 1139-309.

Study dates: Enrollment for PLATO occurred between October 2006 and July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study locations: 862 centers in 43 countries, including the United States (Wallentin et al, 2009a; Wallentin et al, 2009b, supplementary appendix).

Study objective: To assess clinical outcomes in elderly (≥75 years) versus younger (<75 years) patients treated with ticagrelor or clopidogrel (Husted et al, 2011d).

Study design:

- PLATO was a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared ticagrelor to clopidogrel for the prevention of CV events in 18,624 patients with ACS (Wallentin et al, 2009a; James et al, 2009).

Inclusion/exclusion criteria:

Key inclusion criteria:

- Age ≥18 years

- Hospitalization with documented evidence of ACS (UA, NSTEMI, or STEMI) within 24 hours of randomization

Treatment arms/dosing:

- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel:
  - Ticagrelor 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
  - Clopidogrel 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients also received ASA once daily unless intolerant.

Primary endpoints:

- The primary efficacy endpoint was the time to first occurrence of the composite of CV death, MI, or stroke.

- The primary safety endpoint was time to first occurrence of PLATO-defined major bleeding event.

Results:

- The majority of baseline characteristics differed significantly between elderly and younger patients. Differences in final diagnosis and planned management strategy were also noted between age groups and are shown in the following table.

TABLE 3-26: Select Baseline Characteristics, Final Diagnosis, and Planned Management Strategy. Adapted from poster presented at: American College of Cardiology; April 2-5, 2011; New Orleans, LA.

Characteristic	Age ≥75 years n=2878	Age <75 years n=15,744	p-value
Women %	43.5	25.6	<0.0001
Median BMI, kg/m^2 (25th-75th percentile)	26.2 (23.9-29.1)	27.6 (24.9-30.7)	<0.0001
Body weight <60 kg, %	12.0	6.2	<0.0001
CV risk factors, %			
Diabetes	28.1	24.5	<0.0001
Habitual smoker	10.0	40.6	<0.0001
Hypertension	75.2	63.7	<0.0001
Dyslipidemia, including hypercholesterol	46.1	46.8	0.4731
Other medical history, n (%)			
Angina pectoris	53.2	43.4	<0.0001
MI	26.5	19.4	<0.0001
CHF	10.5	4.8	<0.0001
PCI	14.6	13.2	0.0362
CABG	8.9	5.4	<0.0001
TIA	4.8	2.3	<0.0001
Nonhemorrhagic stroke	5.8	3.5	<0.0001
Chronic renal disease	9.8	3.2	<0.0001
Final diagnosis, %			
STEMI	25.9	40.0	<0.0001
NSTEMI	52.6	41.0	
UA	19.1	16.3	
Other	2.4	2.7	
Planned invasive management, % [a]	61.5	73.9	<0.0001
PCI during study	73.2	78.8	<0.0001
Coronary angiography during study	96.6	97.8	0.0036
CABG during study	10.0	10.0	0.9946
Planned noninvasive management, % [a]	38.5	26.1	<0.0001
PCI during study	23.2	30.6	<0.0001
Coronary angiography during study	44.0	58.6	<0.0001
CABG during study	8.1	11.4	0.0017

BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; CV = cardiovascular; NSTEMI = nonST-segment elevation MI; MI = myocardial infarction; PCI = percutaneous intervention; STEMI = ST-segment elevation MI; TIA = transient ischemic attack; UA = unstable angina. [a]Subgroup based on prerandomization strategy.

Efficacy*:*

Association of Age With Clinical Outcomes

- After adjustment for differences in baseline characteristics, irrespective of treatment, age (<75 vs. ≥75 years) was significantly associated with poorer clinical outcomes.
- The rate of the composite primary endpoint was 17.7% in patients ≥75 years of age versus 9.5% in patients <75 years of age (HR: 1.48; 95% CI: 1.32-1.66).

Effect of Ticagrelor and Clopidogrel on Efficacy and Bleeding Outcomes by Age

- In the overall PLATO study population, 9.8% of ticagrelor-treated patients versus 11.7% of clopidogrel-treated patients experienced an event from the composite primary endpoint (HR: 0.84; 95% CI: 0.77-0.92; p<0.001) at 12 months (Wallentin et al, 2009a).
    - When considering the ≥75 years and <75 years patient groups, this treatment effect was independent of age (interaction p-value of 0.22)(Husted et al, 2011).
    - For the secondary efficacy endpoints (all cause mortality, MI, CV death, definite stent thrombosis), the treatment effect was independent of age (<75 vs. ≥75 years; p-value interaction was nonsignificant).

Results are presented in the following table.

TABLE 3-27: Association of Age and Treatment With Efficacy Outcomes. Adapted from poster presented at: American College of Cardiology; April 2-5, 2011; New Orleans, LA.

		KM% at Month 12			
Endpoints	**Total Patients**	**Ticagrelor n=9333**	**Clopidogrel n=9291**	**HR (95% CI)**	**p-value (interaction)**
CV death/MI/Stroke					
≥75 years	471	17.2	18.3	0.94 (0.78-1.13)	0.22
<75 years	1399	8.6	10.4	0.82 (0.74-0.91)	
All-cause Mortality					
≥75 years	293	9.8	12.4	0.81 (0.65-1.03)	0.78
<75 years	608	3.6	4.8	0.78 (0.67-0.92)	
MI					
≥75 years	241	9.3	9.4	0.96 (0.75-1.24)	0.25
<75 years	864	5.4	6.6	0.81 (0.71-0.93)	
CV Death					
≥75 years	242	8.1	10.3	0.79 (0.61-1.02)	0.90
<75 years	549	3.3	4.2	0.81 (0.68-0.95)	
Definite Stent Thrombosis					
≥75 years	25	1.8	2.1	0.66 (0.30-1.45)	0.94
<75 years	141	1.3	1.9	0.67 (0.49-0.93)	

CABG = coronary artery bypass graft; CI = confidence interval; CV= cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.

Safety

- In the overall PLATO study population, the occurrence of major bleeding was similar between the ticagrelor and clopidogrel treatment groups when analyzed according to the PLATO bleeding criteria (11.6% vs. 11.2%, respectively; HR: 1.04, 95% CI: 0.95-1.13, p=0.43) (Wallentin et al, 2009).
    - PLATO-defined major bleeding was similar in both treatment groups and was independent of age (<75 vs. ≥75 years; interaction p-value of 1.00) as shown in the following table (Husted et al, 2011).

TABLE 3-28: Association of Age and Treatment with Safety Outcomes. Adapted from poster presented at American College of Cardiology 60th Annual Scientific Session; April 2-5, 2011; New Orleans, LA.

		KM% at Month 12			
Endpoints	**Total Patients**	**Ticagrelor n=9333**	**Clopidogrel n=9291**	**HR (95% CI)**	**p-value (interaction)**
Major Bleeding					
≥75 years	341	14.2	13.5	1.04 (0.84-1.28)	1.00
<75 years	1545	11.2	10.8	1.04 (1.94-1.15)	
NonCABG Major Bleeding					
≥75 years	183	8.3	7.1	1.16 (0.87-1.55)	0.78
<75 years	482	3.9	3.2	1.22 (1.02-1.46)	

CABG = coronary artery bypass graft; CI = confidence interval; CV= cardiovascular; HR = hazard ratio; KM = Kaplan-Meier.

Association of Age, Management Approach, and Treatment With Outcomes

- The association of age, management approach (planned invasive management vs. planned medical management), and treatment (ticagrelor vs. clopidogrel) with clinical outcomes was analyzed and is shown in the following table.

TABLE 3-29: Association of Age, Management Approach, and Treatment With Outcomes. Adapted from poster presented at: American College of Cardiology 60th Annual Scientific Session; April 2-5, 2011; New Orleans, LA.

	Planned Invasive Management n=13,408			Planned Medical Management n=5216			
	KM %		HR (95% CI)	KM %		HR (95% CI)	p-value interaction
	TCG	CLP		TCG	CLP		
CV Death, MI, Stroke Efficacy							
≥75 years	16.6	15.4	1.09 (0.85-1.38)	17.9	23.0	0.77 (0.59-1.01)	0.0360
<75 years	7.9	9.9	0.80 (0.70-0.90)	10.5	12.0	0.89 (0.74-1.08)	
All-cause Death							
≥75 years	9.3	10.3	0.95 (0.70-1.29)	10.6	15.8	0.67 (0.47-0.94)	0.1647
<75 years	3.2	4.3	0.77 (0.63-0.94)	4.9	6.2	0.81 (0.62-1.07)	
Major Bleeding							
≥75 years	16.6	16.0	1.03 (0.80-1.32)	10.6	9.4	1.11 (0.74-1.67)	0.7143
<75 years	10.8	10.9	0.99 (0.88-1.12)	12.2	10.5	1.18 (0.98-1.43)	
NonCABG-related Major Bleeding							
≥75 years	10.4	8.7	1.20 (0.86-1.67)	5.2	4.5	1.12 (0.62-2.02)	0.5753
<75 years	3.9	3.3	1.17 (0.96-1.44)	3.7	2.9	1.37 (0.95-1.98)	

CABG = coronary artery bypass graft; CI = confidence interval; CLP = clopidogrel; CV= cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; TCG = ticagrelor.

Effect of Ticagrelor and Clopidogrel on Dyspnea and Ventricular Pauses by Age

- Dyspnea was observed more frequently in ticagrelor-treated versus clopidogrel-treated patients. This observation did not differ between age groups.
- In the first week after randomization, but not at 30 days, ventricular pauses were recorded more frequently in the ticagrelor group versus the clopidogrel group, with no difference between age groups.
- Results are shown in the following table.

TABLE 3-30: Dyspnea and Ventricular Pauses by Age and Treatment. Adapted from poster presented at: American College of Cardiology 60th Annual Scientific Session; April 2-5, 2011; New Orleans, LA.

	KM %			
	Ticagrelor n=9333	**Clopidogrel n=9291**	**HR/OR[a] (95% CI)**	**p-value (interaction)**
Dyspnea				
≥75 years	18.8	12.2	1.63 (91.33-1.90)	0.2072
<75 years	14.2	7.8	1.89 (1.70-2.09)	
Ventricular Pauses – First Week[b]				
≥3 seconds				
≥75 years	7.2	6.9	1.06 (0.54-2.08)	0.1408
<75 years	5.5	2.9	1.92 (1.26-2.93)	
≥5 seconds				
≥75 years	2.8	2.7	1.05 (0.36-3.05)	0.2846
<75 years	1.8	0.9	2.14 (1.01-4.55)	
Ventricular Pauses – At 30 Days[c]				
≥3 seconds				
≥75 years	2.4	3.4	0.70 (0.20-2.54)	0.2907
<75 years	2.1	1.3	1.57 (0.73-3.38)	
≥5 seconds				
≥75 years	0.0	1.1	NR	NR
<75 years	1.0	0.5	2.03 (0.61-6.77)	

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; OR = odds ratio; NR = not reported. [a]dyspnea calculated as HR, all other values are OR. [b]ticagrelor group n=1461 and clopidogrel group n=1432; [c]ticagrelor group n=992 and clopidogrel group n=1012.

James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J.* 2010a;31:3006-3016.

James S, Angiolillo DJ, Cornel JH, et al. Supplementary data. *Eur Heart J.* 2010b. Available at: http://eurheartj.oxfordjournals.org/content/suppl/2010/08/27/ehq325.DC1/ehq325supp.pdf. Accessed July 20, 2011.

Study dates: Enrollment for PLATO occurred between October 2006 and July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study locations: 862 centers in 43 countries, including the United States (Wallentin et al, 2009a; Wallentin et al, 2009b).

Study objective: To compare the effect of ticagrelor with that of clopidogrel on the clinical outcomes of patients with DM or poor glycemic control in the PLATO trial (James et al, 2010a).

Study design:
- PLATO was a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared ticagrelor to clopidogrel for the prevention of CV events in 18,624 patients with ACS (Wallentin et al, 2009a; James et al, 2009).

- In the prespecified subgroup analysis, efficacy and safety outcomes of ticagrelor treatment and of clopidogrel treatment were evaluated in relation to DM status, metabolic control, and type of DM (James et al, 2010a).

- The cohort of patients with DM was not powered to show a difference in the primary outcome between the ticagrelor and clopidogrel treatment groups.

- There was no stratification based on DM status, DM type, or degree of glycemic control before randomization.

Inclusion/exclusion criteria: These criteria were the same as those of the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009).

Treatment arms/dosing:
- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel.
  - Ticagrelor 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
  - Clopidogrel 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients also received ASA once daily unless intolerant.

Primary endpoints:
- The primary efficacy endpoint was the time to first occurrence of the composite of death from vascular causes, MI, or stroke.

- The primary safety endpoint was time to first occurrence of PLATO-defined major bleeding event.

Results:

Patient characteristics:
- Baseline characteristics of patients with DM were similar between the ticagrelor and clopidogrel groups (see the following table) (James et al, 2010a; James et al, 2010b).

TABLE 3-31: Baseline Characteristics of Patients With Diabetes Mellitus. Adapted from supplementary data (Table S6). *Eur Heart J*. 2010b; Available at: http://eurheartj.oxfordjournals.org/content/suppl/2010/08/27/ehq325.DC1/ehq325supp.pdf.

Characteristic	Ticagrelor (n=2326)	Clopidogrel (n=2336)	p-value
Median age (25^{th}-75^{th} percentile)	64 years (56-72 years)	64 years (56-72 years)	0.738
% Women	33.9	35.7	0.191
Median BMI (25^{th}-75^{th} percentile)	28.8 (25.7-32.4)	28.4 (25.7-31.9)	0.134
Race			0.747
% Black	2.3	1.9	NR
% Oriental	6.6	7.1	NR
% Caucasian	89.6	89.3	NR
Other	1.5	1.7	NR
% Smokers	24.6	25.0	0.799
% Pts with HTN	81.8	81.3	0.701
% Pts with dyslipidemia	58.5	60.8	0.107
% Pts for whom invasive treatment planned	65.8	67.6	0.188
Final diagnosis[a]			
% NSTEMI	48.4	46.7	NR
% STEMI	28.2	29.2	NR
% UA	20.7	21.1	NR
% Other	2.7	2.9	NR
Median glucose (25^{th}-75^{th} percentile)	9.6 mmol/L (7.1-13.0 mmol/L)	9.9 mmol/L (7.3-13.4 mmol/L)	0.038
Median HbA_{1c} (25^{th}-75^{th} percentile)	7.6% (6.7-8.9%)	7.6% (6.6-9.1%)	0.698
Median CrCL (25^{th}-75^{th} percentile)	76.5 mL/min (58.4-97.0 mL/min)	76.2 mL/min (57.6-96.4 mL/min)	0.568

BMI = body mass index; CrCL = creatinine clearance; HbA_{1c} = hemoglobin A_{1c}; HTN = hypertension; NR = not reported; NSTEMI = non-ST-segment elevation myocardial infarction; Pts = patients; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina. [a] Type of acute coronary syndrome defined using final diagnosis of index event.

- There were no significant differences in the percentages of ticagrelor-treated and clopidogrel-treated diabetic patients who underwent coronary angiography, PCI, or CABG before discharge or during the study (James et al, 2010b). In addition, similar percentages of patients with DM in the ticagrelor and clopidogrel treatment groups underwent implantation of any stent, BMS only, or 1 or more DESs.

- The percentages of ticagrelor-treated diabetic patients did not significantly differ from those of the clopidogrel-treated diabetic patients in terms of use of the following medications from the time of the index event to the end of hospitalization: ASA, beta-blockers, ACE-I, and/or ARBs, statins, calcium channel blockers, diuretics, GP IIb/IIIa inhibitors, insulin (54.8% vs. 55.6%, respectively; p=0.595), and any diabetic medication (84.4% vs. 83.9%, respectively; p=0.642).

Efficacy Results:

- In the overall study population, 9.8% of ticagrelor-treated patients versus 11.7% of clopidogrel-treated patients experienced an event from the composite primary endpoint (HR: 0.84; 95% CI: 0.77-0.92; p<0.001) at 12 months (Wallentin et al, 2009a).

Efficacy Outcomes in Relation to DM Status and Randomized Treatment:

- In patients with DM, the benefit seen with ticagrelor was consistent with the overall trial results, but it did not reach nominal statistical significance (see the following table) (James et al, 2010a).

- A DM status-by-treatment interaction was not found.

Efficacy Outcomes in Relation to Metabolic Control and Randomized Treatment:

- For patients with an HbA_{1c} concentration ≥6% (median value), those treated with ticagrelor had a significantly greater reduction in the primary composite endpoint and all-cause mortality than did those treated with clopidogrel (see the following table). The reduction was 2.8% in the primary composite endpoint and 1.8% in all-cause mortality.

- For patients with a serum glucose concentration ≥6.8 mmol/L (median value), those treated with ticagrelor had significantly greater reductions in the primary composite endpoint and all-cause mortality than did those treated with clopidogrel (see the following table). The reduction was 2.3% in the primary composite endpoint and 1.8% in all-cause mortality.

- No significant treatment-by-glucose- or HbA_{1c}-level interactions were noted.

- Outcomes were consistent across subgroups of diabetic patients with no interactions for the ACS type (ie, STEMI or non-ST-elevation ACS), intended strategy of treatment at the start (ie, invasive or noninvasive treatment), or extent of renal function.

Efficacy Outcomes in Relation to DM Type and Randomized Treatment:

- Patients treated with insulin had greater rates of the primary composite endpoint and all-cause mortality than did diabetic patients who were not treated with insulin (see the following table). Effects of ticagrelor and clopidogrel treatments were consistent with the overall trial results.

- No treatment-by-DM type (ie, insulin-treated/not insulin-treated, or type I/type II DM) interaction was observed.

TABLE 3-32: Efficacy Outcomes in Relation to DM Status, Metabolic Control, DM Type, and Insulin Use in Patients Given Ticagrelor or Clopidogrel. Adapted from *Eur Heart J.* 2010a;31:3006-3016.

Efficacy Outcome	Variable	No. of Patients	% in Ticagrelor Group (n)	% in Clopidogrel Group (n)	HR (95% CI)	p-value (interaction)
Primary composite endpoint[a]	No DM	13,951	8.4 (555)	10.2 (664)	0.83 (0.74-0.93)	0.49
	DM	4662	14.1 (309)	16.2 (350)	0.88 (0.76-1.03)	
	SG <6.8 mmol/L	7604	8.0 (284)	9.7 (346)	0.83 (0.71-0.98)	0.52
	SG ≥6.8 mmol/L	7646	11.7 (428)	14.0 (497)	0.85 (0.74-0.96)	
	HbA_{1c} <6%	7260	8.2 (288)	9.0 (305)	0.93 (0.79-1.09)	0.24
	HbA_{1c} ≥6%	7890	11.4 (419)	14.2 (528)	0.80 (0.70-0.91)	
	DM, no insulin[b]	3625	13.1 (225)	14.2 (243)	0.93 (0.78-1.12)	0.30
	DM, insulin[b]	1036	17.7 (84)	22.8 (106)	0.78 (0.58-1.03)	
	Type I	209	12.4 (13)	16.4 (15)	0.78 (0.37-1.63)	0.73
	Type II	4451	14.2 (296)	16.1 (335)	0.89 (0.76-1.04)	
All-cause mortality	No DM	13,951	3.7 (246)	5.0 (318)	0.77 (0.65-0.91)	0.66
	DM	4662	7.0 (153)	8.7 (188)	0.82 (0.66-1.01)	
	SG <6.8 mmol/L	7604	3.1 (110)	4.1 (142)	0.79 (0.62-1.01)	0.38
	SG ≥6.8 mmol/L	7646	6.0 (218)	7.8 (274)	0.79 (0.66-0.94)	
	HbA_{1c} <6%	7260	3.4 (114)	4.2 (142)	0.79 (0.62-1.01)	0.71
	HbA_{1c} ≥6%	7890	5.6 (206)	7.4 (269)	0.78 (0.65-0.93)	
	DM, no insulin[b]	3625	6.2 (105)	7.8 (133)	0.79 (0.61-1.03)	0.66
	DM, insulin[b]	1036	10.0 (48)	11.7 (54)	0.88 (0.60-1.30)	
	Type I	209	4.6 (5)	3.1 (3)	1.53 (0.37-6.41)	0.39
	Type II	4451	7.2 (148)	9.0 (185)	0.81 (0.65-1.00)	
MI[c]	No DM	13,951	5.0 (329)	6.2 (402)	0.81 (0.70-0.94)	0.32
	DM	4662	8.4 (175)	9.1 (191)	0.92 (0.75-1.13)	
	SG <6.8 mmol/L	7604	5.5 (192)	6.2 (223)	0.87 (0.72-1.06)	0.84
	SG ≥6.8 mmol/L	7646	6.4 (227)	7.9 (273)	0.82 (0.68-0.97)	
	HbA_{1c} <6%	7260	5.1 (179)	5.8 (190)	0.92 (0.75-1.13)	0.47
	HbA_{1c} ≥6%	7890	6.8 (241)	8.2 (299)	0.81 (0.68-0.96)	
Definite stent thrombosis[c]	No DM	8766	1.3 (53)	1.8 (77)	0.68 (0.48-0.97)	0.89
	DM	2518	1.6 (18)	2.4 (29)	0.65 (0.36-1.17)	
	SG <6.8 mmol/L	4383	1.2 (25)	1.0 (23)	1.07 (0.61-1.89)	0.45
	SG ≥6.8 mmol/L	4882	1.5 (33)	2.4 (56)	0.60 (0.39-0.93)	
	HbA_{1c} <6%	4592	1.4 (30)	1.4 (32)	0.91 (0.55-1.50)	0.51
	HbA_{1c} ≥6%	4636	1.3 (28)	2.0 (46)	0.62 (0.39-1.00)	

CI = confidence interval; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; MI = myocardial infarction; NR = not reported; SG = serum glucose. [a] The primary efficacy composite endpoint was the composite of death due to vascular causes, MI, or stroke; [b] Before the index event; [c] Results for DM, no insulin; DM, insulin; type I DM; and type II DM were not provided.

Bleeding Results:

- In the overall study population, the rates of PLATO-defined major bleeding were similar between the 2 treatment groups (11.6% and 11.2% for the ticagrelor- and clopidogrel-treated groups, respectively; p=0.43) (Wallentin et al, 2009a).

Bleeding Outcomes in Relation to DM Status and Randomized Treatment:

- The rates of major bleeding in the ticagrelor and clopidogrel groups, regardless of DM status, were similar (James et al, 2010a). These results are consistent with those of the overall study population.

- Interactions involving bleeding type and definition of bleeding (PLATO or TIMI) were not significant.

- PLATO-defined, non-CABG–related bleeding events were numerically more common in the ticagrelor-treated group of diabetic patients than in the clopidogrel-treated group (see the following table).

- CABG-related bleeding events were numerically more common in the clopidogrel-treated group of diabetic patients than in the ticagrelor-treated group (see the following table).

Bleeding Outcomes in Relation to Metabolic Control and Randomized Treatment: Among patients with HbA_{1c} concentrations ≥6% (median value) and among patients with serum glucose concentrations ≥6.8 mmol/L (median value), those treated with ticagrelor had rates of major bleeding similar to those of patients treated with clopidogrel (see the following table).

Bleeding Outcomes in Relation to DM Type and Randomized Treatment: The incidence of PLATO-defined major bleeding was similar between treatment groups irrespective of insulin use and in patients with type II DM (see the following table) (James et al, 2010a; James et al, 2010c).

TABLE 3-33: Outcomes in Relation to DM Status, Metabolic Control, and DM Type in Patients Given Ticagrelor or Clopidogrel. Adapted from *Eur Heart J.* 2010a;31:3006-3016.

Type of Bleeding	Variable	No. of Patients	% in Ticagrelor Group (n)	% in Clopidogrel Group (n)	HR (95% CI)	p-value (interaction)
PLATO-defined major bleeding	No DM	13,798	10.8 (674)	10.0 (624)	1.08 (0.97-1.20)	0.21
	DM	4621	14.1 (287)	14.8 (305)	0.95 (0.81-1.12)	
	SG <6.8 mmol/L	7604	11.0 (370)	10.4 (364)	1.04 (0.90-1.20)	0.35
	SG ≥6.8 mmol/L	7646	12.0 (412)	11.1 (378)	1.09 (0.94-1.25)	
	HbA_{1c} <6%	7260	10.9 (357)	8.8 (290)	1.22 (1.05-1.43)	0.08
	HbA_{1c} ≥6%	7890	12.3 (428)	12.6 (446)	0.98 (0.86-1.12)	
	DM, no insulin[a]	3593	13.8 (217)	14.7 (241)	0.91 (0.76-1.09)	0.28
	DM, insulin[a]	1027	15.1 (70)	15.1 (64)	1.12 (0.80-1.58)	
	Type I DM	208	18.0 (19)	11.1 (10)	1.79 (0.83-3.86)	0.08
	Type II DM	4412	13.9 (268)	14.9 (295)	0.92 (0.78-1.09)	
Non-CABG–related major bleeding (PLATO-defined)[b]	No DM	13,798	4.1 (253)	3.4 (208)	1.22 (1.01-1.46)	0.69
	DM	4621	5.5 (109)	4.9 (98)	1.13 (0.86-1.49)	
	SG <6.8 mmol/L	7604	3.9 (126)	3.4 (117)	1.10 (0.86-1.42)	0.97
	SG ≥6.8 mmol/L	7646	4.9 (168)	3.9 (129)	1.30 (1.03-1.64)	
	HbA_{1c} <6%	7260	4.2 (132)	2.9 (96)	1.36 (1.05-1.77)	0.47
	HbA_{1c} ≥6%	7890	4.8 (163)	4.2 (144)	1.16 (0.93-1.46)	
CABG-related major bleeding (PLATO-defined)[b]	No DM	13,798	6.8 (430)	7.1 (441)	0.97 (0.85-1.11)	0.51
	DM	4621	9.3 (189)	10.4 (213)	0.90 (0.74-1.09)	
	SG <6.8 mmol/L	7604	7.4 (252)	7.4 (258)	1.00 (0.84-1.19)	0.32
	SG ≥6.8 mmol/L	7646	7.5 (254)	7.7 (261)	0.97 (0.81-1.15)	
	HbA_{1c} <6%	7260	6.9 (230)	6.3 (206)	1.10 (0.91-1.33)	0.31
	HbA_{1c} ≥6%	7890	8.0 (278)	8.8 (313)	0.91 (0.77-1.07)	
TIMI-defined major bleeding[b]	No DM	13,798	7.6 (476)	7.0 (434)	1.10 (0.96-1.25)	0.10
	DM	4621	9.0 (181)	9.9 (204)	0.90 (0.74-1.10)	
	SG <6.8 mmol/L	7604	7.7 (261)	7.2 (247)	1.09 (0.91-1.29)	0.07
	SG ≥6.8 mmol/L	7646	7.9 (269)	7.9 (268)	1.00 (0.84-1.18)	
	HbA_{1c} <6%	7260	7.5 (247)	6.3 (207)	1.18 (0.98-1.42)	0.05
	HbA_{1c} ≥6%	7890	8.2 (287)	8.7 (306)	0.96 (0.82-1.13)	

CABG = coronary artery bypass graft; CI = confidence interval; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; PLATO = PLATelet inhibition and patient Outcomes; SG = serum glucose; TIMI = Thrombolysis in Myocardial Infarction. [a]Before the index event; [b]Results for DM, no insulin; DM, insulin; type I DM; and type II DM were not provided.

Storey RF, Becker RC, Cannon CP, et al. Ticagrelor does not affect pulmonary function tests compared to clopidogrel in acute coronary syndromes: results of the PLATO pulmonary substudy [abstract and poster]. Poster presented at: 59th Annual Scientific Session of the American College of Cardiology (ACC) held jointly with the ACC i2 Summit; March 14-16, 2010; Atlanta, GA. *J Am Coll Cardiol.* 2010c;55:E1007. Abs A108.

Study dates: Recruitment for the PLATO trial, of which the pulmonary substudy was a part, lasted from October 2006 through July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study location: The patients who participated in the pulmonary substudy were treated at 5 centers in 15 countries (United States, Poland, India, Hungary, and the Czech Republic) (Storey et al, 2010c).

Study objective: To assess the effects of ticagrelor versus clopidogrel on forced expiratory volume in 1 second (FEV_1) after completion of study treatment

Study design:
- This substudy of pulmonary function was a component of PLATO, a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared ticagrelor to clopidogrel for the prevention of CV events in 18,624 patients with ACS (Wallentin et al, 2009a; James et al, 2009).

- Pulmonary function tests (PFTs) were performed after receiving 30-40 days of study medication, repeated within 10 days before the end of treatment, and repeated again 20-30 days after discontinuation of treatment.

Key inclusion/exclusion criteria: Patients had to be enrolled in PLATO to participate in the substudy. Patients with advanced lung disease, symptomatic heart failure, or recent CABG surgery were excluded (Storey et al, 2010c).

Treatment arms/dosing:
- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel:
  - Ticagrelor 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
  - Clopidogrel 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients received ASA once daily unless intolerant.

Endpoints: The primary endpoint was FEV_1 after completion of study treatment.

Results:
- One hundred ninety-nine patients (101 in the ticagrelor group and 98 in the clopidogrel group) participated in the substudy.

- Both groups had similar FEV_1 results at the different time points, with no apparent change over time or after discontinuation of study medication. Results of other PFT parameters also did not significantly differ between groups, with no apparent change over time or after discontinuation of study medication (shown in the following table).

- Six patients in the ticagrelor group and 8 patients in the clopidogrel group had an AE of dyspnea or an event associated with dyspnea (such as CHF or COPD exacerbation).

TABLE 3-34: Effects of Ticagrelor and Clopidogrel on Pulmonary Function in ACS Patients.[a,b] Adapted from *J Am Coll Cardiol.* 2010;55(suppl 1): A108.E1007.

	Ticagrelor (n=101)	Clopidogrel (n=98)
FEV_1 pre-beta agonist (L)	2.81±0.73	2.70±0.84
FEV_1 post-beta agonist (L)	2.74±0.73	2.66±0.79
$FEF_{25\%-75\%}$ (%)	2.90±1.26	2.62±1.33
SpO_2 (%)	97±3	96±2
TLC (L)	6.42±1.28	6.27±1.36
FRC (L)	3.56±0.86	3.47±0.94
RV (L)	2.72±0.85	2.54±0.89
DLCO (%)	7.00±1.77	7.18±2.60

ACS = acute coronary syndromes; DLCO = diffusing capacity of the lung using carbon monoxide; $FEF_{25\%-75\%}$ = forced expiratory flow measured as 25% and 75% of the FVC; FEV_1= forced expiratory volume in 1 second; FRC = functional residual capacity; FVC = forced vital capacity; RV = residual volume; SD = standard deviation; SpO_2 = pulse oximeter oxygen saturation; TLC = total lung capacity. [a] Data are mean ± SD; [b] The p-values are nonsignificant for all parameters.

Storey RF, Becker RC, Harrington RA, et al. Increased incidence of dyspnoea associated with ticagrelor did not appear to adversely affect cardiovascular outcomes in the PLATO study [abstract and poster]. Poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden. *Eur Heart J*. 2010d;31(abstract suppl):203. Abstract P1352.

Study dates: Recruitment for the PLATO trial, of which the pulmonary substudy was a part, lasted from October 2006 through July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Study objective: To determine the incidence of dyspnea and its relationship with safety and efficacy outcomes (Storey et al, 2010d).

Study design:

- This study was a subanalysis of PLATO trial data from 9235 patients in the ticagrelor group and 9186 patients in the clopidogrel group (each of whom had received at least 1 dose).

- Episodes of dyspnea between the time of enrollment and the last scheduled study visit and the suspected etiology of the dyspnea episodes were reported. Dyspnea events unresolved at the end of the final visit were considered ongoing.

Inclusion/exclusion criteria: Criteria were the same as those of the overall PLATO trial (Wallentin et al, 2009a; James et al, 2009).

Treatment arms/dosing:

- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel:
  - Ticagrelor 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
  - Clopidogrel 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- Patients received ASA once daily unless intolerant.

Results:

- Dyspnea was reported as an AE for 1339 (14.5%) of patients in the ticagrelor group and 798 (8.7%) of patients in the clopidogrel group (Storey et al, 2010d).
  - Fifteen percent of these dyspnea cases in the ticagrelor group and 6.9% in the clopidogrel group ($p<0.0001$) were considered related to the study drug.
  - Severe dyspnea occurred in 39 (0.4%) of ticagrelor-treated patients and in 24 (0.3%) of clopidogrel-treated patients.
  - Discontinuation of study medication due to dyspnea occurred for 79 (5.9%) in the ticagrelor group with dyspnea and for 13 (1.6%; $p<0.0001$) in the clopidogrel group with dyspnea.
  - Ongoing dyspnea at the end of the study was reported for 5.0% of ticagrelor-treated patients and for 3.1% of clopidogrel-treated patients ($p<0.0001$).

- Reported etiologies of dyspnea that occurred during treatment are shown in the following table.

TABLE 3-35: Reported Etiologies of On-treatment Dyspnea. Adapted from poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden.

Reported Etiology of Dyspnea	% Pts in Ticagrelor Group	% Pts in Clopidogrel Group
Unexplained/unknown	27.3	20.1
HF due to cardiac etiology	23.7	30.8
COPD	6.0	5.3
Asthma	1.0	0.8

COPD = chronic obstructive pulmonary disease; HF = heart failure; pts = patients.

- Patients with dyspnea in either treatment group were more likely than those without dyspnea to have a greater waist circumference, be older, and/or have a history of smoking, dyspnea, asthma, COPD, or chronic renal disease.

- The median time to dyspnea onset (on and off treatment) was significantly earlier in patients treated with ticagrelor than in those treated with clopidogrel (23 vs. 43 days; p<0.0001).

- The 12-month efficacy and safety outcomes of patients with dyspnea were compared with those of patients without dyspnea (see the following table).
  - The Kaplan-Meier incidences of the primary composite endpoint (ie, rate of MI, stroke, or CV death) and MI at 12 months were significantly greater in those with dyspnea than in those without dyspnea in either treatment group.
  - No significant effect on stroke, CV death, or total mortality was identified for patients who reported dyspnea in either treatment group.
  - Major bleeding was significantly more common in those with dyspnea than in those without dyspnea in the ticagrelor treatment group (p=0.033). Major or minor bleeding occurred significantly more often in patients with dyspnea than in those without this AE in either treatment group (p≤0.002).

TABLE 3-36: Efficacy and Safety Outcomes at 12 Months for Patients With Dyspnea at Any Time After Randomization and for Those Without Dyspnea in the Ticagrelor and Clopidogrel Treatment Groups. Adapted from poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden.

	Ticagrelor Group (n=9235)			Clopidogrel Group (n=9186)		
Endpoint	**No. (K-M%) With Dyspnea (n=1339)**	**No. (K-M%) Without Dyspnea (n=7896)**	**p-value**	**No. (K-M%) With Dyspnea (n=798)**	**No. (K-M%) Without Dyspnea (n=8388)**	**p-value**
Efficacy						
Primary composite[a]	151 (11.9)	701 (9.4)	0.014	117 (15.7)	882 (11.2)	0.001
MI	112 (8.7)	393 (5.4)	<0.0001	83 (11.3)	515 (6.6)	<0.0001
Stroke	21 (1.7)	102 (1.4)	0.506	9 (1.3)	95 (1.2)	0.946
CV death	39 (3.3)	306 (4.1)	0.061	37 (4.8)	391 (5.0)	0.885
Total mortality	47 (3.9)	342 (4.6)	0.117	48 (6.4)	443 (5.7)	0.472
PLATO-defined Bleeding						
Major bleeding[b]	164 (13.7)	797 (11.2)	0.033	96 (13.5)	833 (11.0)	0.091
Major or minor bleeding[c]	256 (21.4)	1083 (13.7)	<0.0001	136 (18.8)	1079 (14.2)	0.002

CV = cardiovascular; K-M = Kaplan-Meier; MI = myocardial infarction; PLATO = PLATelet inhibition and patient Outcomes. [a] The primary composite endpoint was the rate of MI, stroke, or CV death. [b] Major bleeding refers to that defined for the PLATO study: life-threatening bleeding or bleeding that lead to significant disability or to a drop in hemoglobin ≥ 3.0 g/dL but < 5.0 g/dL or necessitating a transfusion of 2 or 3 units of red cells. [c] Minor bleeding was defined in the PLATO trial as bleeding for which medical intervention was required but did not meet major-bleeding criteria.

- The following table shows a comparison of the 12-month Kaplan-Meier rates of key efficacy endpoints between patients with dyspnea in the ticagrelor group and those with dyspnea in the clopidogrel group.

TABLE 3-37: Twelve-month Kaplan-Meier Rates of Key Efficacy Endpoints for Patients With Dyspnea in the Ticagrelor Group and in the Clopidogrel Group. Adapted from poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden.

	12-Month Kaplan-Meier Rate (%)		
Endpoint	**Ticagrelor**	**Clopidogrel**	**p-value**
Primary composite	11.9	15.7	0.02
MI	8.7	11.3	0.096
CV death	3.3	4.8	0.035

CV = cardiovascular; MI = myocardial infarction.

- The incidences of clinical outcomes during Days 31 through 360 for those who experienced dyspnea within the first 30 days after randomization were determined (see the following table).

- Compared with the patients who experienced dyspnea within 30 days after randomization to the clopidogrel group, those randomized to the ticagrelor group had significantly lower incidences of CV death and total mortality from Day 31 onward (see the following table).

TABLE 3-38: Incidence of Clinical Outcomes From Day 31 to Day 360 for Patients Who Experienced Dyspnea Within the First 30 Days After Randomization. Adapted from poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden.

	Ticagrelor		Clopidogrel			
Outcome	**No. of pts**	**No. of Pts With Events (K-M%)**	**No. of pts**	**No. of Pts With Events (K-M%)**	**HR (95% CI)**	**p-value**
Primary composite	697	53 (8.4)	314	34 (11.7)	0.68 (0.44, 1.05)	0.079
MI	701	37 (5.9)	314	15 (5.2)	1.07 (0.59, 1.96)	0.813
Stroke	722	7 (1.1)	331	5 (1.7)	0.62 (0.20, 1.95)	0.414
CV death	726	16 (2.6)	331	21 (7.0)	0.34 (0.18, 0.64)	0.001
Total mortality	726	19 (3.0)	331	26 (8.5)	0.32 (0.18, 0.58)	0.0002

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction; Pts = patients. [a] The primary composite endpoint was the rate of MI, stroke, or CV death.

Scirica BM, Cannon CP, Emanuelsson H, et al. The incidence of bradyarrhythmias and clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (PLATelet inhibition and patient Outcomes) trial. Results of the continuous electrocardiographic assessment substudy. *J Am Coll Cardiol.* 2011;57:1908-1916.

Study dates: Recruitment for the PLATO trial, of which this substudy was a part, lasted from October 2006 through July 2008. Follow-up ended in February 2009 (Wallentin et al, 2009a).

Objectives: To perform continuous electrocardiography (cECG) monitoring in a subset of patients from the PLATO trial to determine whether ticagrelor increased the risk of ventricular pauses and whether these pauses were associated with any clinical bradycardic events

Study design:

- This was a prospective analysis of a subgroup of patients from the PLATO trial who had cECG monitoring.

- The PLATO trial was a multinational, prospective, randomized, double-blind, double-dummy, parallel-group, event-driven study that evaluated ticagrelor vs. clopidogrel for the prevention of vascular events in 18,624 patients with ACS (Wallentin et al, 2009a; James et al, 2009).
- Patients at increased risk for bradycardic events were excluded from the PLATO trial. Patients with previously documented syncope suspected to be related to bradycardia but treated with a pacemaker were included in the trial.

- cECG recordings (digital, 3-lead) were initiated after the first dose of study medication and continued for 7 days (Scirica et al, 2011). Patients with a baseline cECG assessment also received another 7-day recording 1 month after randomization.

Patients:

- 2908 patients were included in the cECG analysis, of whom 2866 (98.5%) had 1 week recordings, 1991 (68.4%) had 1 month recordings, and 1949 (67%) had recordings at both1 week and 1 month.

- The median duration of cECG monitoring was 6.2 days during week 1 after randomization and 6.8 days at 1 month.

- There were no important differences between treatment groups in terms of baseline characteristics, planned invasive therapy and concomitant medications known to potentially affect SA or AV nodal function. About 90% of patients received beta blockers and many received 1 or more additional agents including nondihydropyridine calcium antagonists or antiarrhythmic agents.

Treatment arms/dosing:

- Patients were randomized within 24 hours of their ACS event to either ticagrelor or clopidogrel (Wallentin et al, 2009a; James et al, 2009).
  - Ticagrelor 90 mg twice daily
    - Patients randomized to ticagrelor received an initial LD of 180 mg.
    - Patients in the ticagrelor treatment arm who were undergoing PCI over 24 hours after randomization received an additional LD of ticagrelor 90 mg.
  - Clopidogrel 75 mg once daily
    - Patients randomized to clopidogrel who had not received a LD of clopidogrel, or had not been taking clopidogrel or ticlopidine for ≥5 days prior to randomization, received an initial 300 mg LD of clopidogrel as their first dose.
    - Patients in the clopidogrel treatment arm who were undergoing PCI could receive an additional 300 mg LD of clopidogrel at the discretion of the investigator, irrespective of the time in relation to randomization.

- In addition, patients also received ASA 75-100 mg once daily unless intolerant. In patients who were not previously receiving ASA, the preferred LD was 325 mg. In patients with stents, dosage up to 325 mg was permitted for 6 months after stent placement.

Endpoints:

cECG Arrhythmia Endpoints:

- The principal endpoint was the incidence of ventricular pauses ≥3 seconds which was chosen on the basis of guidelines which recommend consideration of pacemaker placement in symptomatic patients with evidence of 3 second pauses (Scirica et al, 2011).

- Other endpoints included the incidence of ventricular pauses lasting at least 5 seconds, the incidence of ventricular tachycardia and supraventricular tachycardia (any episode at >100 beats/min lasting at least 4 beats), and other bradyarrhythmias such as sinus bradycardia (at least 4 beats ≤45 beats/min) or dropped beats (no ventricular beat within 180% of the previous RR interval).

Clinical Arrhythmia Endpoints:

- AEs that could be related to bradycardic events based on prespecified, preferred AE terms

- Investigator-reported symptomatic events that were possibly bradycardic

- Information about the suspected etiology of syncope AEs and reasons for pacemaker insertion

Safety Results:

- There was a significantly higher incidence of ventricular pauses ≥3 seconds in the first weekin the ticagrelor group compared with the clopidogrel group as noted in the following table. At 1 month, pauses ≥3 seconds were reported less frequently and the rate was similar between treatment groups.

- Most events were ventricular pauses of sinoatrial origin and considered asymptomatic and transient in nature. There was a peak in the frequency of ventricular pauses at night in the ticagrelor group that was less evident in the clopidogrel group.

- There was no difference between ticagrelor and clopidogrel in the incidence of clinically reported bradycardic AEs, including syncope, pacemaker placement, and cardiac arrest (see table below).

TABLE 3-39: Arrhythmias at Visit 1 and Visit 2.[a,b] Adapted from *J Am Coll Cardiol*. 2011;57:1912.

Characteristic	Visit 1 (Week 1)			Visit 2 (Day 30)		
	TCG 90 mg BID (n=1451)	CLP 75 mg QD (n=1415)	RR (95% CI)	TCG 90 mg BID (n=985)	CLP 75 mg QD (n=1006)	RR (95% CI)
Heart rate (beats/min)	68.6±10.70	68.5±10.43	NA	68.1±10.16	67.9±10.17	NA
Patients with ≥1 bradyarrhythmia[c]	812 (56.0)	737 (52.1)	1.07[d] (1.00-1.15)	565 (57.4)	506 (50.3)	1.14[e] (1.05-1.24)
Ventricular pauses ≥3 s	84 (5.8)	51 (3.6)	1.61[f] (1.14-2.26)	21 (2.1)	17 (1.7)	1.26 (0.67-2.38)
AV node pause	20 (1.4)	17 (1.2)	1.15 (0.60-2.18)	6 (0.6)	8 (0.8)	0.77 (0.27-2.20)
SA node pause	63 (4.3)	31 (2.2)	1.98[e] (1.30-3.03)	17 (1.7)	11 (1.1)	1.58 (0.74-3.35)
Other pause	7 (0.5)	7 (0.5)	0.98 (0.34- 2.77)	0	0	NR
Ventricular pauses ≥5 s	29 (2.0)	17 (1.2)	1.66 (0.92-3.01)	8 (0.8)	6 (0.6)	1.36 (0.47-3.91)
AV node pauses	9 (0.6)	9 (0.6)	0.98 (0.39-2.45)	2 (0.2)	2 (0.2)	1.02 (0.14-7.24)
SA node pause	22 (1.5)	7 (0.5)	3.06[g] (1.31-7.15)	7 (0.7)	4 (0.4)	1.79 (0.52-6.09)
Other pause	0	3 (0.2)	NR	0	0	NR
Dropped beats	452 (31.2)	416 (29.4)	1.06 (0.95-1.18)	292 (29.6)	266 (26.4)	1.12 (0.97-1.29)
Bradycardia	575 (39.6)	535 (37.8)	1.05 (0.96-1.15)	409 (41.5)	378 (37.6)	1.11 (0.99-1.23)
Patients with ≥1 tachyarrhythmia	1014 (69.9)	961 (67.9)	1.03 (0.98-1.08)	605 (61.4)	623 (61.9)	0.99 (0.93-1.06)
Supraventricular tachyarrhythmia	844 (58.2)	781 (55.2)	1.05 (0.99-1.12)	528 (53.6)	551 (54.8)	0.98 (0.90-1.06)
Ventricular tachyarrhythmia	522 (36.0)	503 (35.5)	1.01 (0.92-1.12)	211 (21.4)	217 (21.6)	0.99 (0.84-1.17)

CI = confidence interval; CLP = clopidogrel; NA = not applicable; NR = not reported; RR = relative risk; s = seconds; TCG = ticagrelor. [a]Data are expressed as n (%) or mean ± standard deviation. [b]p values as noted below, all other p values are >0.05; [c]pause, dropped beat or episode of bradycardia; [d]p=0.04; [e] p=0.002; [f]p=0.006; [g]p=0.008.

TABLE 3-40: AEs of Interest by Ventricular Pause Duration. Adapted from *J Am Coll Cardiol*. 2011;57:1914.

AE, n (%)	All Patients		Patients With Ventricular Pauses ≥3 s		Patients With Ventricular Pauses ≥5 s	
	Ticagrelor n=1472	Clopidogrel n=1436	Ticagrelor n=89	Clopidogrel n=62	Ticagrelor n=32	Clopidogrel n=20
Patients with ≥1 AE of interest[a]	148 (10.1)	126 (8.8)	23 (25.8)	16 (25.8)	10 (31.3)	8 (40.0)
Dizziness	38 (2.6)	41 (2.9)	1 (1.1)	2 (3.2)	0	1 (5.0)
Hypotension	51 (3.5)	37 (2.6)	3 (3.4)	5 (8.1)	1 (3.1)	2 (10.0)
Bradycardia	61 (4.1)	36 (2.5)	16 (18.0)	7 (11.3)	7 (21.9)	4 (20.0)
Syncope	5 (0.3)	2 (0.1)	1 (1.1)	1 (1.6)	1 (3.1)	1 (5.0)
Cardiac arrest	3 (0.2)	6 (0.4)	2 (2.2)	2 (3.2)	1 (3.1)	1 (5.0)
Heart block	6 (0.4)	15 (1.0)	3 (3.4)	5 (8.1)	1 (3.1)	1 (5.0)
Loss of consciousness	0	2 (0.1)	0	0	0	0
Pacemaker placement[b]	7 (0.5)	14 (1.0)	5 (5.6)	5 (8.1)	3 (9.4)	2 (10)
Presyncope	0	0	0	0	0	0
Vasovagal syncope	3 (0.2)	1 (0.1)	0	0	0	0

AE = adverse event; s = second. [a] Patients could report in more than 1 AE category; [b]Patients could be counted in both temporary and permanent pacemaker placement categories, but each patient was counted only once for "pacemaker placement." Pacemaker placement included not only those pacemakers reported as AEs but also those recorded as a bradycardic events.

Phase II Studies

Cannon C, Husted S, Harrington RA, et al. Safety, tolerability and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol*. 2007;50:1844-1851.

Study dates: Study entry occurred between October 3, 2004, and April 23, 2005.

Study locations: In this study, 152 sites in 14 countries participated.

Study objective: To assess the safety, tolerability, and initial efficacy of AZD6140 (ticagrelor) plus ASA compared with clopidogrel plus aspirin in patients with non-ST-segment elevation (NSTE) ACS.

Study design: The Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction-2 (DISPERSE-2) trial was a randomized, double-blind, double-dummy trial.

Inclusion/exclusion criteria:

Key inclusion criteria:

- Age ≥18 years
- Hospitalized for NSTE-ACS in past 48 hours
- Ischemic symptoms at rest ≥10 minutes
- Biochemical marker evidence of MI or ECG evidence of ischemia

Key exclusion criteria:

- ST segment elevation lasting at least 20 minutes
- More than 48 hours from onset of symptoms
- PCI or index event resulting from PCI within 48 hours before randomization,
- No significant coronary stenosis detected by angiography, and/or
- Conditions associated with an increased risk of bleeding (eg, GI bleeding within the previous 6 months, hemorrhagic disorder).

Treatment arms/dosing:

- Patients (n=990) were randomized to
  - ticagrelor 90 mg BID,
  - ticagrelor 180 mg BID, or
  - clopidogrel 300 mg followed by 75 mg QD.
- Patients in the ticagrelor group were further randomized to receive or not receive an initial 270 mg LD.
- Treatment continued for 1, 2, or 3 months, depending on the timing of enrollment during the trial period, and follow-up visits were conducted monthly.
- All patients received standard medical and interventional treatment for ACS, including ASA at an initial dose of 325 mg, followed by 75 to 100 mg daily with or without a GP IIb/IIIa inhibitor.
- Patients undergoing PCI within 48 hours after randomization could be given an additional 300 mg LD of clopidogrel (or placebo) at the discretion of the treating physician.

Endpoints:

- The primary endpoint of the study was the rate of major or minor bleeding through 4 weeks. Bleeding definitions are provided in the following table.

TABLE 3-41: DISPERSE-2 Bleeding Definitions. Adapted from Online Appendix for *J Am Coll Cardiol*. 2007;50:1844-1851.

Term		Associated Decrease in Hemoglobin	Transfusion of Whole Blood or PRBCs for Bleeding
Major bleed—life threatening[a] meets any one of these criteria:	• Fatal • Intracranial • Intrapericardial with cardiac tamponade • Hypovolemic shock or severe hypotension requiring pressors or surgery	>5 g/dL (3.1 mmol/L)	≥4 units
Major bleed—other meets any one of these criteria:	Significantly disabling (eg, intraocular with permanent vision loss)	3-5 g/dL (1.9-3.1 mmol/L)	2-3 units
Minor bleed	Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)	—	1 unit
Minimal bleed	All others not requiring intervention or treatment (eg, bruising, bleeding gums, oozing from injection sites)		

PRBCs = packed red blood cells. [a] Based on the TIMI major bleeding category.

- The Independent Clinical Adjudication Committee also prospectively classified bleeding according to the definitions used in the CURE trial (Yusuf et al, 2001), as well as TIMI criteria (Bovill et al, 1991) and GUSTO criteria (GUSTO investigators, 1993).

- Additional endpoints of the trial were 1) individual and composite incidence of MI (including silent MI), death, stroke, and severe recurrent ischemia; and 2) incidence of recurrent ischemia with ticagrelor plus ASA and clopidogrel plus ASA using total duration of ischemia as detected by continuous Holter monitoring during the first 4 to 7 days after randomization (Cannon et al, 2007).

Results:

Patients:

- A total of 491 patients (50%) were scheduled to receive study drug for 12 weeks, 243 (25%) for 8 weeks, and 250 (25%) for 4 weeks.

- Of the enrolled patients, the mean age was 63 years; ≥33% were women; 24% had diabetes mellitus; 48% had ST-segment depression ≥0.5 mm; and 62% had NSTE MI.

- Angiography was performed in 67% of patients, 42% had PCI, and 9% underwent CABG.

Endpoints:

- The primary endpoint of protocol-defined major or minor bleeding occurred in 26 patients (8.1%) in the clopidogrel group, 32 patients (9.8%) in the ticagrelor 90 mg BID group, and in 25 patients (8.0%) in the ticagrelor 180 mg BID group (p=0.43 and p=0.96, respectively, vs. clopidogrel).

- The rates of major bleeding events were not different between groups; however, there were 2 fatal bleeds, both in the ticagrelor 90 mg BID group. More detailed bleeding results are shown in the following table.

TABLE 3-42: Bleeding Events in DISPERSE-2.[a] Adapted from *J Am Coll Cardiol*. 2007;50:1846.

Bleeding	Clopidogrel 75 mg QD (n=327)	Ticagrelor 90 mg BID (n=334)	p-value vs. Clopidogrel	Ticagrelor 180 mg BID (n=323)	p-value vs. Clopidogrel
Through Week 4					
Total	26 (8.1)	32 (9.8)	0.43	25 (8.0)	0.96
Major	22 (6.9)	23 (7.1)	0.91	16 (5.1)	0.35
Major—fatal/life threatening	14 (4.4)	11 (3.4)	0.53	10 (3.2)	0.44
Major—other	8 (2.5)	12 (3.7)	0.38	6 (1.9)	0.61
Minor	4 (1.3)	9 (2.7)	0.18	12 (3.8)	0.0504
Through Week 12					
Total	30 (9.9)	34 (10.9)	0.62	33 (11.4)	0.72
Major	26 (8.7)	26 (8.6)	0.96	20 (6.3)	0.32
Major—fatal/life threatening	16 (5.4)	13 (4.5)	0.55	14 (4.3)	0.61
Major—other	10 (3.3)	13 (4.2)	0.54	6 (1.9)	0.34
Minor	4 (1.3)	9 (2.7)	0.18	16 (6.1)	0.01

[a] Values are n (%). Total bleeding is defined as major or minor bleeding. The number of events to the 2 time points is given with a Kaplan-Meier percent estimate of the event rate. Because follow-up ranged from 4 to 12 weeks, incidence rates and Kaplan-Meier event rates differ. Statistical testing was done by using a Cox proportional hazards model.

- The most common type of bleeding was epistaxis, followed by periprocedural hemorrhage or hematoma.

- Of the total number of bleeding episodes, 73% were procedure-related in the clopidogrel group, 53% in the ticagrelor 90 mg BID group, and 52% in the ticagrelor 180 mg BID group. Additional bleeding results are shown in the following table.

TABLE 3-43: Additional Bleeding Results in DISPERSE-2.[a] Adapted from *J Am Coll Cardiol*. 2007;50:1847.

Bleeding	Clopidogrel 75 mg QD	Ticagrelor 90 mg BID	Ticagrelor 180 mg BID
Gastrointestinal bleeding	3 (0.9%)	7 (2.1%)	4 (1.2%)
Discontinuation of study drug due to bleeding	3 (0.9%)	8 (2.4%)	5 (1.5%)
Blood transfusions[b]	22 (6.7%)	24 (7.2%)	15 (4.6%)
Protocol-defined minimal bleeding (nonadjudicated)	70 (21%)	89 (27%)[c]	100 (31%)[d]

[a] Values are n (%). [b] The median number of units transfused was 3 (interquartile range, 2-4 Units). [c] p=0.12 vs. clopidogrel. [d] p=0.006 vs. clopidogrel.

- Assessment of bleeding by LD showed that major bleeding within the first 48 hours occurred in 8 patients receiving clopidogrel (2.4%), compared with 3 (1.8%) receiving ticagrelor 90 mg BID, 2 (1.3%) receiving ticagrelor 180 mg BID, and in 6 (1.8%) receiving ticagrelor 270 mg as a LD.

- Similar rates of death or CV death were observed in all groups. A numerical trend toward a lower rate of MI was observed in the ticagrelor groups. Detailed clinical endpoint results are shown in the following table.

TABLE 3-44: Clinical End Points in DISPERSE-2.[a] Adapted from *J Am Coll Cardiol*. 2007;50:1848.

Endpoint, %	Clopidogrel 75 mg Daily (n=327)	Ticagrelor 90 mg BID (n=334)	p-value vs. Clopidogrel	Ticagrelor 180 mg BID (n=329)	p-value vs. Clopidogrel
Through Week 4, n (%)					
All-cause death	2 (0.6)	6 (1.9)	0.18	3 (1.0)	0.64
CV death	2 (0.6)	6 (1.9)	0.18	3 (1.0)	0.64
MI	11 (3.5)	7 (2.2)	0.34	3 (1.0)	0.047
Stroke	1 (0.3)	2 (0.6)	0.57	0 (0.0)	0.99
Severe recurrent ischemia	2 (0.6)	2 (0.6)	0.99	4 (1.3)	0.41
Recurrent ischemia	5 (1.6)	10 (3.2)	0.21	4 (1.6)	0.98
CV death/MI/stroke	12 (3.8)	14 (4.3)	0.71	6 (1.9)	0.17
Through Week 12, n (%)					
All-cause death	4 (1.3)	7 (2.4)	0.38	6 (1.7)	0.72
CV death	4 (1.3)	6 (1.9)	0.54	6 (1.7)	0.72
MI	15 (5.6)	12 (3.8)	0.41	8 (2.5)	0.06
Stroke	1 (0.3)	2 (0.6)	0.57	0 (0.0)	0.99
Severe recurrent ischemia	3 (1.4)	5 (2.3)	0.50	9 (3.7)	0.09
Recurrent ischemia	9 (3.0)	13 (4.9)	0.29	9 (3.4)	0.78
CV death/MI/stroke	17 (6.2)	19 (6.0)	0.90	11 (3.5)	0.12

[a] None of these rates were statistically different between groups. The number of events to the 2 time points is given, with a Kaplan-Meier % estimate of the event rate. Because follow-up ranged from 4-12 weeks, incidence rates and Kaplan-Meier event rates differ. Statistical testing was done by using a Cox proportional hazards model.

- Higher rates of nausea, dyspepsia, and hypotension were reported in the ticagrelor groups.
- Dyspnea was reported in 21 patients (6.4%) in the clopidogrel group, 35 (10.5%) in the ticagrelor 90 mg BID group ($p=0.07$ vs. clopidogrel), and in 51 (15.8%) in the ticagrelor 180 mg BID group ($p<0.0002$ vs. clopidogrel).
- Resolution of dyspnea occurred within 24 hours in 27% of patients reporting this symptom, and after 24 hours in 25% of patients.
- Dyspnea persisted greater than 15 days in 48% of patients. The overall incidence of persistent dyspnea was 2% for clopidogrel and 6% in both ticagrelor groups.
- Study discontinuation occurred in 6%, 6%, and 7% of patients receiving clopidogrel, ticagrelor 90 mg BID, and ticagrelor 180 mg BID, respectively. Additional information regarding reported AEs is provided in the following table.

TABLE 3-45: Crude Incidence Rates of Investigator-Reported AEs.[a] Adapted from *J Am Coll Cardiol*. 2007;50:1849.

	Clopidogrel 75 mg Daily (n=327)	Ticagrelor 90 mg BID (n=334)	p-value vs. Clopidogrel	Ticagrelor 180 mg BID (n=323)	p-value vs. Clopidogrel
Dyspnea	21 (6.4)	35 (10.5)	0.07	51 (15.8)	<0.0002
Chest pain	29 (8.9)	25 (7.5)	0.57	24 (7.4)	0.57
Headache	28 (8.6)	32 (9.6)	0.69	21 (6.5)	0.37
Nausea	11 (3.4)	22 (6.6)	0.07	21 (6.5)	0.07
Dyspepsia	9 (2.8)	16 (4.8)	0.22	10 (3.1)	0.82
Insomnia	9 (2.8)	18 (5.4)	0.12	15 (4.6)	0.22
Diarrhea	11 (3.4)	10 (3.0)	0.83	24 (7.4)	0.02
Hypotension	2 (0.6)	14 (4.2)	0.004	12 (3.7)	0.01
Dizziness	10 (3.1)	14 (4.2)	0.53	11 (3.4)	0.83
Syncope	2 (0.6)	4 (1.2)	0.69	5 (1.5)	0.28
Rash	2 (0.6)	3 (0.9)	1.00	6 (1.9)	0.17

[a]Values are n (%). The rates are crude incidences of the number of patients divided by the total number of patients in the safety cohort. Median exposure was approximately 2 months. Statistical testing was done with the Fisher exact test.

- An arrhythmia analysis was performed in 885 patients (89.4% of all enrolled patients).
  - The rates of ventricular tachycardias were similar in all treatment groups.
  - A greater number of mostly asymptomatic ventricular pauses lasting >2.5 seconds(s) were detected post hoc in the ticagrelor groups compared to the clopidogrel group.
  - In patients who experienced pauses lasting >5 seconds, 7 were due to sinus block or sinus node exit block, and 4 were due to complete heart block.
  - Detailed results of the arrhythmia analysis are shown in the following table.

TABLE 3-46: Arrhythmia Events Detected on cECG Monitoring Begun at Randomization.[a] Adapted from *J Am Coll Cardiol*. 2007;50:1849.

	Clopidogrel 75 mg QD (n=297)	Ticagrelor 90 mg BID (n=305)	Ticagrelor 180 mg BID (n=283)	p-value[b]
VT				
Patients with sustained VT >30 seconds	1 (0.3)	0 (0.0)	1 (0.3)	0.49, 1.00
Patients with ≥1 NSVT	65 (22)	67 (22)	74 (26)	1.00, 0.24
Patients with ≥1 triplet	93 (31)	89 (29)	77 (27)	0.59, 0.32
Ventricular Pauses				
Patients with ≥1 pause >2.5 seconds	13 (4.3)	17 (5.5)	28 (9.9)	0.58, 0.014
Patients with >3 episodes of pauses >2.5 seconds	1 (0.3)	6 (2.0)	14 (4.9)	0.12, <0.001
Patients with at least 1 pause >5 seconds	1 (0.3)	5 (1.6)	6 (2.1)	0.22, 0.06

NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia. [a] Values are n (%). [b] The p values were calculated with Fisher exact test. The first compares ticagrelor 90 mg BID vs. clopidogrel, and the second compares ticagrelor 180 mg BID vs. clopidogrel. VT was categorized into sustained VT (lasting > 30 seconds), NSVT (≥ 4 beats and < 30 seconds in length), and triplets (3 ventricular beats). A ventricular pause was defined as either sinus or ventricular pause that resulted in the absence of a QRS complex that lasted > 2.5 seconds.

3.1.2 PUBLISHED AND UNPUBLISHED STUDIES FOR OFF-LABEL INDICATIONS

Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J.* 2006;27:1038-1047.

Study dates: Randomization occurred from September 2003 to December 2003.

Study locations: The study was conducted at 13 sites in Hungary, Norway, and Denmark.

Study objective: The DISPERSE (Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction) study assessed the PD, PK, safety, and tolerability of ticagrelor with ASA relative to clopidogrel with ASA in patients with atherosclerotic disease.

Study design: Randomized, double-blind, double-dummy, multinational study

Inclusion/exclusion criteria:

Key inclusion criterion: Treatment with ASA (75-100 mg once daily) for confirmed astherosclerotic disease for at least 2 weeks before randomization

Key exclusion criteria:

- Recent ACS
- PCI with balloon or stent
- Conditions with increased risk of bleeding
- SCr ≥1.2× the upper limit of normal
- Hemoglobin ≥5% below the lower limit of normal

Treatment arms/dosing:

- Patients received 28 days of one of the following treatments:
  - Ticagrelor 50 mg BID (n=41),
  - Ticagrelor 100 mg BID (n=39),
  - Ticagrelor 200 mg BID (n=37),
  - Ticagrelor 400 mg QD (n=46), or
  - Clopidogrel 75 mg QD (n=37).
- All patients received ASA 75-100 mg QD.

Results:

PK results:

- Plasma concentrations of ticagrelor and AR-C124910XX were stable and predictable at steady state.
- Plasma concentrations of ticagrelor and AR-C124910XX increased linearly and in proportion to the dose administered on Day 1. At Day 28, relative to the 50 mg and 100 mg BID doses, slightly greater than dose-proportional PK and correspondingly lower total plasma oral clearance (CL/F) were observed with ticagrelor 200 mg BID and ticagrelor 400 mg QD.
- At steady state (achieved by Day 14), AR-C124910XX exposure was approximately 35% of that of ticagrelor.
- C_{max} and AUC for ticagrelor and AR-C124910XX did not vary significantly with age (≤65 or >65 years) or gender.

Safety results:

- The most common AE was bleeding, which increased in incidence with the 3 higher doses of ticagrelor (vs. ticagrelor 50 mg BID or clopidogrel). GI hemorrhage with decreased hemoglobin was reported in a patient receiving ticagrelor 400 mg QD.

- Other commonly reported AEs were dyspnea, dizziness, and headache. The incidence of dyspnea appeared to increase with increasing dose of ticagrelor. None of the reports of dyspnea was considered serious or associated with heart failure or bronchospasm.

- Uric acid levels increased by 5%-10% in all ticagrelor groups and decreased by approximately 10% in the clopidogrel group.

- No deaths were reported in the trial.

Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation*. 2009;120:2577-2585.

Study dates: Patients were enrolled between October 2007 and March 2009.

Study locations: The study was conducted at 8 institutions in the United States and the United Kingdom.

Study objective: To compare the onset and offset of the antiplatelet effects of ticagrelor, clopidogrel, and placebo in patients with stable CAD

Study design: Phase II, multicenter, randomized, double-blind, double-dummy, parallel-group study

Inclusion:
- Age ≥18 years
- Stable CAD
- ASA 75-100 mg/day

Exclusion:
- History of ACS in prior 12 months
- Any indication for antithrombotic therapy
- CHF
- LVEF <35%
- FEV_1 or FVC below LLN
- Bleeding diathesis
- Severe pulmonary disease
- Pregnancy
- Smoker
- Treatment with moderate or strong P450 3A inhibitors, substrates or strong P450 3A inducers
- PLT <100,000/mm^3
- Hb <10 g/dL
- HbA_{1c} ≥10%
- History of drug addiction or alcohol abuse in past 2 years
- NSAID
- CrCL <30 mL/min

Treatment arms/dosing:
- Eligible patients on clopidogrel therapy prior to screening underwent a minimum 14-day washout period before randomization.
- Patients were randomized to receive either a ticagrelor 180 mg loading dose, followed by 90 mg twice daily (n=57); clopidogrel 600 mg loading dose, followed by 75 mg once daily (n=54); or placebo (n=12) for 6 weeks.
- Following the 6-week treatment phase, patients entered a 10-day drug-offset period during which they were given a final dose of the study drug on the first day of the offset period.
- In addition, all patients continued to receive treatment with ASA 75-100 mg once daily throughout the study.

Endpoints:

Primary Endpoint:
- Onset: IPA (ADP 20 µM/L, final extent) 2 hours after the loading dose
- Offset: The rate of offset (slope) of the antiplatelet effect curve as assessed by IPA (ADP 20 µM/L, final extent) between 4 and 72 hours after the last dose.
- Platelet aggregation was measured by light-transmittance aggregometry.

Results:

Onset:

- Two hours post-loading dose, IPA (ADP 20 µM/L, final extent) was 88% and 38% for ticagrelor and clopidogrel, respectively ($p<0.0001$).
- Two hours post-loading dose, IPA (ADP 20 µM/L, maximum extent) was 65% and 25% for ticagrelor and clopidogrel, respectively ($p<0.0001$); the mean time to maximum IPA (ADP 20 µM/L, final extent) was 2 hours and 7.8 hours, respectively.
- One half hour post-loading dose, IPA was 41% and 8% for ticagrelor and clopidogrel, respectively, and remained greater during all time points during the first 24 hours ($p<0.0001$).
- Within 1 hour post-loading dose, IPA for ticagrelor was greater than the maximum IPA after the clopidogrel loading dose ($p<0.0001$).
- Within 2 hours post-loading dose, a greater proportion of patients achieved >50% IPA (98% vs. 31%; $p<0.0001$) and >70% IPA (90% vs. 16%, $p<0.0001$) in the ticagrelor group versus the clopidogrel group, respectively.
- $P2Y_{12}$ reaction units (PRU) and platelet reactivity index (PRI) were significantly lower with ticagrelor at all time points during the study except ≥48 hours after the final dose ($p<0.0001$).
- Platelet receptor expression was significantly lower with ticagrelor at all time points during the study except ≥48 hours after the final dose ($p<0.05$).

Offset:

- The rate of offset (slope) of the antiplatelet effect curve from 4 to 72 hours after the last dose was greater in the ticagrelor group than in the clopidogrel group (-1.04 vs. -0.48 IPA %/h; $p<0.0001$).
- At 24 and 48 hours after the last dose, mean IPA was similar for ticagrelor and clopidogrel (p=NS). At 72 and 120 hours after the last dose, mean IPA was significantly lower ($p\leq0.05$) with ticagrelor. Mean IPA did not differ between groups thereafter.
- The time required for IPA to decrease from 30% to 10% in the ticagrelor group was less than half that in the clopidogrel group (53 vs. 116 hours, respectively), and the time to reach 10% was nearly twice as long after clopidogrel discontinuation (109 vs. 196 hours, respectively).
- IPA for ticagrelor on Day 3 after the last dose was comparable to clopidogrel at Day 5; IPA on Day 5 for ticagrelor was similar to clopidogrel on Day 7 and did not differ from placebo (p=NS).
- PRU and PRI were significantly lower with ticagrelor at all time points during the study except ≥48 hours after the final dose ($p<0.001$).

Safety:

- Bleeding-related events occurred more frequently in the ticagrelor group than in the clopidogrel and placebo groups (28.1% vs. 13.0% and 8.3%, respectively). There were no major bleeding events. There was 1 clinically relevant minor bleed in the placebo group; the remaining events were classified as minor (1 event in the ticagrelor group) or minimal.
- Dyspnea determined by the investigator to be likely or possibly due to the study drug occurred in 25%, 4%, and 0% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively (ticagrelor vs. clopidogrel, $p<0.01$).
- Five patients (ticagrelor [n=4]; placebo [n=1]) discontinued study treatment due to an AE; this included 3 patients discontinuing due to dyspnea in the ticagrelor group.

Gurbel PA, Bliden KP, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation.* 2010b;121:1188-1199.

Study dates: Patients were enrolled between May 2008 and March 2009.

Study locations: The study was conducted at 10 sites in North America and Europe.

Study objective: To investigate the antiplatelet effect of ticagrelor in clopidogrel nonresponders and responders and to study platelet function during switching from clopidogrel to ticagrelor therapy and vice versa in patients with stable CAD treated with aspirin

Study design: Phase II, multicenter, randomized, double-blind, double-dummy, 2-way crossover study

Inclusion:
- Stable CAD
- ASA 75-100 mg QD
- Age ≥18 years

Exclusion:
- History of ACS within past 12 months
- History of bleeding diathesis or severe pulmonary disease
- Pregnancy
- Smoking >1 pack per day
- Concomitant therapy within 14 days: strong CYP3A inhibitors or inducers, antithrombotic therapy other than ASA
- NSAID use
- PLT <100,000 mm^3
- Hb <10 g/dL
- Hb A_{1c} ≥10%
- CrCL <30 mL/min
- History of drug addiction or alcohol abuse in past 2 years

Treatment arms/dosing:
- All patients received concomitant aspirin (75-100 mg daily) during the study.

- Period 1:
  - Nonresponders and responders were randomized to:
    - Ticagrelor 180 mg LD followed by 90 mg twice daily for 14 days
    - Clopidogrel 600 mg LD followed by 75 mg once daily for 14 days

- Period 2:
  - All patients in the nonresponders group crossed over to the other treatment for an additional 14 days.
  - One-half of the patients in the responders group continued on the same treatment while the remaining patients switched to the other treatment for an additional 14 days.
  - Patients who switched treatments received a loading dose followed by the maintenance dose.

Endpoints:
- Both final extent of aggregation and maximal extent of aggregation were measured in response to ADP 20 µM/L (In House Data).

- Responsiveness to clopidogrel was based on absolute change in IPA (ADP 20 µM/L, maximal extent) 6-8 hours after a 300 mg LD of clopidogrel.
  - Nonresponders were defined by a ≤10% absolute change in IPA.
  - Responders were defined by a >10% absolute change in IPA.

- Cut points for on-treatment high platelet reactivity were >59% for platelet aggregation (ADP 20 µM/L, maximal extent), ≥235 PRU for the VerifyNow $P2Y_{12}$ assay, and >50% PRI for the VASP phosphorylation assay.

- Proportion of clopidogrel nonresponders who responded to ticagrelor (defined as patients with IPA, final extent, >10% at 4 hours) was the primary endpoint (In House data) .

- Comparisons of IPA, PRU, PRI, platelet receptor expression, platelet reactivity, and antiplatelet effects in ticagrelor versus clopidogrel were also evaluated.

Results:

Nonresponder Cohort (n=41):

- The proportion of clopidogrel nonresponders who achieved >10% final extent IPA on ticagrelor treatment was not significantly different from the proportion achieving this target on clopidogrel treatment (In House Data).

- A greater proportion of clopidogrel nonresponders achieved >10% maximum extent IPA on ticagrelor compared with clopidogrel (p=0.005).

- A greater proportion of clopidogrel nonresponders achieved >30% and >50% maximum extent IPA on ticagrelor versus clopidogrel (p<0.05 for both).

TABLE 3-47: Nonresponder Cohort: Percentage of Patients Who Responded to Ticagrelor Versus Clopidogrel at 4 Hours After the Last Maintenance Dose. *Circulation.* 2010;121:1191.

Decrease from Baseline in Platelet Aggregation[a]	Ticagrelor		Clopidogrel		Ticagrelor vs. Clopidogrel		McNemar Test
	Patients, %	95% CI	Patients, %	95% CI	Patients, %	95% CI	p-value
>10%	100	89-100	75	57-89	25	8-41	0.005
>30%	75	57-89	13	4-29	62	42-79	<0.001
>50%	13	4-29	0	0-11	13	1-23	0.046

ADP = adenosine diphosphate; CI = confidence interval. [a]Platelet aggregation induced by ADP 20 µmol, maximum extent. Decrease from baseline = percent pretreatment aggregation minus percent post-treatment aggregation.

- When switched from clopidogrel to ticagrelor, platelet aggregation decreased from 59±9% to 35±11% (p<0.0001).

- When switched from ticagrelor to clopidogrel, platelet aggregation increased from 36±14% to 56±9% (p<0.0001).

- Results from the VerifyNow™ $P2Y_{12}$ assay showed significantly lower platelet reactivity at all time points during ticagrelor treatment compared to clopidogrel treatment with the exception of the first hour in the initial crossover period (p≤0.05).

Responder Cohort: (n=57):

- Platelet aggregation (ADP 20 µM, maximum extent) was lower after ticagrelor versus clopidogrel in Period 1 (26±9% vs. 49±16%; p<0.0001 at Day 1, 4 hours; 25±11% vs. 47±15%, p<0.0001 at Day 14, 4 hours) and after crossing over in Period 2 (24±9% vs. 37±10%; p<0.001 at Day 1, 4 hours; 32±8% vs. 45±8%; p<0.001 at Day 14, 4 hours).

- IPA was significantly higher at all time points with ticagrelor loading and maintenance therapy (p<0.05) except Period 2, Day 15, 0 hours. After switching from clopidogrel, IPA was maximal within 1 hour after the loading dose of ticagrelor.

- Maximum IPA was achieved within 1 hour of switching from clopidogrel to ticagrelor.

- Significantly lower PRU levels were observed during ticagrelor treatment versus clopidogrel treatment with the exception of the first hour of the initial crossover period (p≤0.05).

TABLE 3-48: Responders Versus Nonresponders: Antiplatelet Effect of Ticagrelor and Clopidogrel. *Circulation.* 2010;121:1197.

	Responder LSM (95% CI)	Nonresponder LSM (95% CI)	Responders vs. Nonresponders	
			Difference (95% CI)	p-value
IPA (ADP 20 µmol/L, maximum extent)				
Ticagrelor	57 (51-63)	50 (43-57)	7 (-2 to 16)	0.114
Clopidogrel	34 (28-40)	21 (14-28)	13 (4 to 21)	0.004
VerifyNow-PRU				
Ticagrelor	39 (15-64)	59 (31-86)	-20 (-55 to -16)	0.270
Clopidogrel	182 (157-206)	245 (218-273)	-64 (-99 to -29)	0.0004
VASP-PRI				
Ticagrelor	15 (9-21)	20 (14-27)	-5 (-13 to -3)	0.240
Clopidogrel	47 (42-53)	61 (54-67)	-13 (-21 to -5)	0.003

ADP = adenosine diphosphate; CI = confidence interval; IPA = inhibition of platelet aggregation; LSM = least squares mean; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction unit; VASP = vasodilator-stimulated phosphoprotein phosphorylation. Note: for the responder cohort, both Period 1 and 2, Day-14, 4-hour data were used. For the crossover treatment groups, both Period 1 and 2, Day 14, 4-hour data were used. For stay-on-treatment groups, only Period 1, Day 14, 4-hour data were used.

High Platelet Reactivity:

- 98%-100% of ticagrelor patients had platelet reactivity below the cut point versus 44%-70% of clopidogrel patients (as measured by platelet aggregation, VerifyNow $P2Y_{12}$ assay, and VASP phosphorylation).

Safety:

- Five serious AEs—including MI, hypotension, atrial fibrillation, and bradycardia—occurred in 4 patients (nonresponders [n=2], responders [n=2] during or after treatment with ticagrelor).

- One death occurred 30 days after therapy with ticagrelor, but it was not considered to be related to treatment.

- Four bleeding events (major [n=1], minor [n=3]) occurred with ticagrelor treatment. No bleeding events occurred with clopidogrel treatment.

- Dyspnea occurred in 17 patients (ticagrelor [n=13], clopidogrel [n=4]). Most episodes of dyspnea occurred early in the study, resolved without intervention, and did not result in discontinuation.

Storey RF, Bliden KP, Patil SB. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol*. 2010e;56:185-193.

Study dates: Entry into the study occurred between October 17, 2007, and March 5, 2009.

Study locations: Multiple centers in the United Kingdom and the United States

Study objective: To determine whether treatment with ticagrelor was associated with any substantial change in cardiopulmonary function.

Study design: The incidence of dyspnea was evaluated in a 6-week, prespecified subanalysis (n=123) of the ONSET/OFFSET trial, which evaluated platelet inhibition in patients with stable CAD treated with low-dose ASA.

Key inclusion/exclusion criteria: For this subanalysis, patients were required to have received at least 1 dose of study drug. Patients with CHF or significant lung disease were excluded from this subanalysis.

Treatment arms/dosing: Treatment was the same as that in the overall ONSET/OFFSET study (Gurbel et al, 2009).

- Initial LD (Day 1):
  - TCG 180 mg x 1, or
  - CLP 600 mg x 1, or
  - Placebo

- Maintenance doses: TCG 90 mg or placebo in the evening on Day 1, followed by:
  - TCG 90 mg BID (n=57), or
  - CLP 75 mg QD (n=54), or
  - Placebo (n=12) for 6 weeks.

- All patients received ASA 75-100 mg QD.

- Following the 6-week treatment phase, patients entered a 10-day drug-offset period during which they were given a final dose of the study drug on the first day of the offset period.

Results:

- The incidence of dyspnea was 38.6% in the ticagrelor 90 twice daily group ($p<0.001$ vs. clopidogrel), 9.3% in the clopidogrel group, and 8.3% in the placebo group (ticagrelor vs. clopidogrel, $p<0.001$; ticagrelor vs. placebo, $p<0.05$) (Storey et al, 2010e). Dyspnea led to premature discontinuation in 3 patients in the ticagrelor group and no patients in the clopidogrel group.

- Most instances were mild and/or lasted less than 24 hours. In the ticagrelor group, 8 of 22 patients experienced dyspnea within 24 hours and 17 of 22 patients experienced dyspnea 1 week after administration.

- Dyspnea persisted in a few patients through the study follow-up period, which lasted for 10 days after the discontinuation of study medication (n=1, placebo; n=3, ticagrelor; n=3, clopidogrel).

- In patients who experienced dyspnea, no significant changes from baseline to 6 weeks were noted in any of the cardiac measures (blood pressure, heart rate, ECG, left ventricular ejection fraction, or N-terminal pro-brain natriuretic peptide [BNP]) or pulmonary function parameters (such as FEV_1, forced vital capacity [FVC]; FEV_1/FVC, mean forced expiratory flow measured as $FEF_{25\%-75\%}$, total lung capacity (TLC), residual volume, tidal volume, or oxygen saturation).

- Maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC_{0-8}) were similar between ticagrelor-treated patients who experienced dyspnea and those who did not experience dyspnea.

Butler K, Wei C, Teng R. Single-dose ticagrelor does not prolong the QT interval in healthy subjects. *Int J Clin Pharmacol Ther.* 2010;48:643-651.

Study dates: Dates were not reported.

Study location: A single center in Sweden

Study objective: To assess whether a single 900-mg dose of ticagrelor affects the time interval of ventricular depolarization and repolarization (QT interval) in healthy male subjects

Study design: The study was a randomized, double-blind, single-center, single-dose, positive-control, 3-period crossover trial. A total of 36 subjects were randomly assigned to 1 of 6 treatment sequences for each of the following treatments:

- Treatment A: single doses of ticagrelor 900 mg with moxifloxacin placebo
- Treatment B: single doses of moxifloxacin 400 mg with ticagrelor placebo
- Treatment C: single doses of ticagrelor placebo with moxifloxacin placebo

Washout periods of 7 to 14 days were used between treatments. Continuous, 12-lead, resting, digital ECGs were collected over 24 hours after each treatment and corrected for the effect of heart rate on the QT interval by using a study-specific factor (QTcX).

Inclusion and exclusion criteria:

Inclusion criteria:

- Healthy males
- Aged 18-45 years
- Body mass index=20-28 kg/m^2

Exclusion criteria:

- Abnormal ECG at screening or enrollment
- History of arrhythmia or QT interval prolongation
- Heart rate <50 bpm at screening
- QT interval >450 milliseconds for QT intervals corrected for heart rate using Fredericia correction (QTcF) or >480 milliseconds for QT intervals corrected for heart rate using the Bazett correction (QTcB)
- History of heart block.

Endpoints: The primary endpoint was QTcX, which was the QT corrected by using a study-specific factor.

Results:

- No relationship between plasma levels of ticagrelor or its metabolite AR-C124910XX and QT interval was observed.
- A single dose of ticagrelor 900 mg did not prolong the QT interval in healthy subjects.

Butler K, Renli T. Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with mild hepatic impairment. *J Clin Pharmacol*. 2011; 51:978-987.

Study dates and location: Dates and location were not reported in the article.

Study objective: To compare the PK of ticagrelor and the active metabolite (AR-C124910XX) in volunteers with mild hepatic impairment versus healthy controls

Study design: Single-center, nonrandomized, open-label, parallel-group, single-dose study

Inclusion/exclusion criteria:

Key inclusion criteria:

- Men or women 18 years or older
- Weight ≥50 kg
- Body mass index=18-35 kg/m^2
- Confirmation of stable hepatic impairment

Key exclusion criteria:

- Child-Pugh class B or C impairment
- Weight <50 kg
- Presence/history of condition effecting drug disposition
- Any clinically significant ECG findings, laboratory results, or coagulation abnormalities

Treatment arms/dosing: After an overnight fast, all volunteers received a single 90 mg dose of ticagrelor.

Results:

PK and PD results:

- Absorption of ticagrelor and formation of the active metabolite, AR-C124910XX, were rapid in both groups. Ticagrelor exposure was higher in hepatically impaired volunteers (C_{max}: 12%; area under the plasma concentration–time curve from time 0 to infinity [$AUC_{0-\infty}$]: 23%) versus controls. AR-C124910XX exposure was also higher in hepatic impairment (C_{max}: 17%; $AUC_{0-\infty}$: 66%).The unbound fraction of ticagrelor was comparable between groups (see the following table).
- Of note, for unclear reasons, marked interindividual variation in PK parameters was observed for 3 volunteers with hepatic impairment who had much higher exposure to ticagrelor and AR-C12491-XX compared with other subjects in the study.
- A nonsignificant trend towards higher mean inhibition of final extent platelet aggregation using ADP 20 μM was observed in the mild hepatic impairment group versus the control group.
- The concentration-effect profiles overlapped for volunteers with mild hepatic impairment and controls for ticagrelor+AR-C124910XX concentrations up to 200 ng/mL. Although a limited data set, at higher concentrations, the final-extent IPA appeared to be higher in the group with mild hepatic impairment compared to volunteers with normal hepatic function.
- Overall, increased exposure of ticagrelor and AR-C124910XX was not associated with clinically significant changes in PD.

TABLE 3-49: PK Parameters Following a Single 90 mg Dose of Ticagrelor.

PK Parameters[a]	Volunteers With Normal Hepatic Function n=10	Volunteers With Mild Hepatic Impairment n =10	GLS Mean Ratio: Point Estimate (90% CI)[b]
Ticagrelor			
C_{max}, ng/mL	581 (32)	651 (55)	1.12 (0.84-1.51)
AUC_{0-t}, ng*h/mL	3405 (42)	4674 (60)	1.37 (0.93-2.02)
AUC, ng*h/mL[c]	3690 (41)	4964 (65)	1.23 (0.84-1.80)
$t_{1/2}$, h[c]	12 (37)	15 (86)	NR
t_{max}, h	2.0 (1.0-3.0)	2.0 (1.0-4.0)	NR
fu	0.1 (7.6)	0.1 (14.7)	NR
AR-C124910XX			
C_{max}, ng/mL	159 (21)	186 (38)	1.17 (0.92-1.50)
AUC_{0-t}, ng*h/mL	1242 (20)	2022 (46)	1.63 (1.23-2.15)
AUC, ng*h/mL	1304 (18)	2165 (52)	1.66 (1.23-2.24)
$t_{1/2}$, h	10 (21)	15 (76)	NR
t_{max}, h	2.0 (2.0-3.0)	2.0 (2.0-4.0)	NR
Metabolite/Parent Ratios			
C_{max} ratio	0.29 (0.10)	0.30 (0.08)	NR
AUC_{0-t} ratio	0.39 (0.13)	0.45 (0.13)	NR
AUC ratio[c]	0.38 (0.14)	0.45 (0.12)	NR

AUC = area under the curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to last measurable; CI = confidence interval; C_{max} = maximum concentration; fu = unbound fraction; GLS = geometric least squares; NR = not reported; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half–life; t_{max} = time to c_{max}. [a] Values are geometric mean (% coefficient of variation) for C_{max}, AUC_{0-t}, AUC, $t_{1/2}$ and fu; median (range) for t_{max}; mean (standard deviation) for metabolite/parent ratios; [b] GLS mean ratio = mildly impaired/normal; [c] n = 9 in the normal hepatic function group.

Safety results: Ticagrelor was well tolerated; no AEs were reported in the study.

Butler K, Mitchell PD, Teng R. No effects of gender and age on the pharmacokinetics and pharmacodynamics of AZD6140, the first reversible oral P2Y12 receptor antagonist [abstract]. *AAPS J*. 2008;10 (S2). Abs T3002. Available at: http://www.aapsj.org/abstracts/AM_2008/AAPS2008-002925.PDF. Accessed July 20, 2011.

Study dates and location: Dates and location were not provided in the abstract.

Study objective: To determine the effects of gender and age on the PK and PD of ticagrelor in healthy subjects.

Study design: Open-label, parallel-group study of the PK and PD of a single 200 mg oral dose of ticagrelor in men and women of various ages (18 to 45 years and ≥65 years)

Inclusion/exclusion criteria:
Inclusion:
- Healthy men and women
- Age ranges: 18-45 years, ≥65 years of age

Exclusion: Exclusion criteria were not provided.

Treatment arms/dosing: A single 200 mg dose of ticagrelor was given orally after an overnight fast.

Treatment groups were the following:
- 10 men aged 18-45 years,
- 10 women aged 18-45 years,
- 10 men aged ≥65 years,
- 10 women aged ≥65 years.

Results:
- $AUC_{0\text{-}inf}$
  - Ticagrelor $AUC_{0\text{-}inf}$ was 37% higher for women than for men.
  - Ticagrelor $AUC_{0\text{-}inf}$ was 52% higher for eldery subjects than for younger ones.
  - Similar patterns were observed for the active metabolite AR-C124910XX.
- C_{max}
  - Ticagrelor C_{max} was 52% higher for women that for men.
  - Ticagrelor C_{max} was 63% higher for elderly subjects than for younger ones.
  - Similar patterns were observed for the active metabolite AR-C124910XX.
- IPA
  - >90% mean final-extent inhibition was achieved by 4 hours after dose administration in all groups.
  - Final-extent inhibition and maximal-extent inhibition were as follows, respectively:
    - 99.5% and 73.3% in young men
    - 97.3% and 68.3% in young women
    - 94.7% and 65.6% in elderly men
    - 92.9% and 58.7% in elderly women.
- Safety and tolerability: Gender- or age-related differences in safety and tolerability of ticagrelor were not apparent.

Additional Information

Additional trials that are listed on the National Institutes of Health web site clinicaltrials.gov and are recruiting or have not yet started recruiting subjects are the following:

- Evaluation of the Drug-drug Interaction Between Ticagrelor and Venlafaxine When Taken Together in Healthy Volunteers. ClinicalTrials.gov Identifier: NCT01350921. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01350921?term=ticagrelor&rank=6. Accessed July 20, 2011.
- Extended Drug Utilization Study Among Patients Exposed to Ticagrelor, Clopidogrel and Prasugrel. ClinicalTrials.gov Identifier: NCT01276275. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01276275?term=ticagrelor&rank=9. Accessed July 20, 2011.
- Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS). ClinicalTrials.gov Identifier: NCT01225562. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01225562?term=ticagrelor&rank=3. Accessed July 20, 2011.
- A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention (PCI). ClinicalTrials.gov Identifier: NCT01347580. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01347580?term=ticagrelor&rank=2. Accessed July 20, 2011.
- Study to Assess Safety and Efficacy of Ticagrelor (AZD6140) Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation Acute Coronary Syndromes (ACS). ClinicalTrials.gov Identifier: NCT01294462. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01294462?term=ticagrelor&rank=5. Accessed July 20, 2011.
- Ticagrelor Versus Prasugrel in Acute Coronary Syndromes After Percutaneous Coronary Intervention. ClinicalTrials.gov Identifier: NCT01360437. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01360437?term=ticagrelor&rank=3. Accessed July 20, 2011.
- Ticagrelor and Aspirin for the Prevention of Cardiovascular Events After Coronary Artery Bypass Surgery. ClinicalTrials.gov Identifier: NCT01373411. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01373411?term=ticagrelor&rank=7. Accessed July 20, 2011.

3.1.3 CLINICAL EVIDENCE TABLE SPREADSHEET

3.1.3.1 Published & Unpublished Studies for Labeled Indications

TABLE 3-50: Summary Table of Key Studies for Ticagrelor (BRILINTA) Labeled Indications

<table>
<tr><th>Study/Citation</th><th>Study Design</th><th>Treatment/N</th><th>Inclusion/Exclusion Criteria</th><th>Endpoints</th><th>Results</th></tr>
<tr><td colspan="6">Phase III Studies</td></tr>
<tr><td colspan="6">Efficacy and Safety Data</td></tr>
<tr>
<td>PLATO

Wallentin et al. N Engl J Med. 2009a;361:1045-1057.</td>
<td>Phase III multinational, randomized, double-blind, double-dummy, event-driven study conducted in 43 countries.

Aim: to determine whether TCG is superior to CLP for the prevention of vascular events and death in a broad population of patients presenting with ACS.</td>
<td>N=18,624

• TCG 180 mg x 1, then 90 mg BID, or
• CLP 300 mg x 1, then 75 mg QD

Patients received a LD of CLP if they had not been taking CLP or TCG for ≥5 days prior to randomization.

Patients undergoing PCI:
• Additional 90 mg of TCG if >24 hrs after randomization.
• Additional 300 mg of CLP at the discretion of the investigator, irrespective of the time in relation to randomization.

ASA 75-100 mg QD unless intolerant.

ASA 325 mg QD for ASA-naive patients and after stent placement (up to 6 months).

Follow-up: 12-months. The median duration of exposure to study drug was 277 days (IQR: 179-365 days).</td>
<td>Inclusion:
Hospitalized for ACS with or without STE, with onset during the previous 24 hours AND ≥2 of the following:
• ST-segment changes on ECG indicating ischemia
• Positive biomarker indicating myocardial necrosis
• One of the following:
○ ≥60 years of age
○ Previous MI or CABG
○ CAD with ≥50% stenosis in ≥2 vessels
○ Previous ischemic stroke, TIA (hospital-based diagnosis), carotid stenosis (≥50%), or cerebral revascularization
○ Diabetes mellitus
○ Peripheral artery disease
○ Chronic renal dysfunction

OR either of the following:
○ Persistent STE ≥1 mm (not known to be pre-existing or due to a coexisting disorder) in ≥2 contiguous leads plus primary PCI planned
○ New LBBB plus primary PCI planned

Exclusion:
• Contraindication to CLP or</td>
<td>Primary Efficacy:
• Time to first occurrence of any event from the composite of death from vascular causes, MI, or stroke

Secondary Efficacy:
• Composite of death from any cause, MI, or stroke
• Composite of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event
• MI
• Death from CV causes
• Stroke
• Death from any cause

Primary Safety:
• Time to first occurrence of any major bleeding event

Secondary Safety:
• Minor bleeding
• Dyspnea
• Arrhythmia
• Ventricular pauses
• Unanticipated AEs
• Laboratory safety results</td>
<td>
<table>
<tr><th>Efficacy Endpoints N (%)</th><th>TCG</th><th>CLP</th><th>HR (95% CI)</th><th>p-value</th></tr>
<tr><td>Primary</td><td>n=9333</td><td>n=9291</td><td></td><td></td></tr>
<tr><td>CV death, MI, stroke</td><td>864 (9.8)</td><td>1014 (11.7)</td><td>0.84 (0.77-0.92)</td><td><0.001</td></tr>
<tr><td>Secondary</td><td>n=9333</td><td>n=9291</td><td></td><td></td></tr>
<tr><td>Total death, MI, stroke</td><td>901 (10.2)</td><td>1065 (12.3)</td><td>0.84 (0.77-0.92)</td><td><0.001</td></tr>
<tr><td>CV death, MI, stroke, recurrent ischemia, TIA, arterial thrombotic event</td><td>1290/9333 (14.6)</td><td>1456/9291 (16.7)</td><td>0.88 (0.81-0.95)</td><td><0.001</td></tr>
<tr><td>MI</td><td>504 (5.8)</td><td>593 (6.9)</td><td>0.84 (0.75-0.95)</td><td>0.005</td></tr>
<tr><td>CV death</td><td>353 (4.0)</td><td>442 (5.1)</td><td>0.79 (0.69-0.91)</td><td>0.001</td></tr>
<tr><td>Stroke</td><td>125 (1.5)</td><td>106 (1.3)</td><td>1.17 (0.91-1.52)</td><td>0.22</td></tr>
<tr><td>Total death</td><td>399 (4.5)</td><td>506 (5.9)</td><td>0.78 (0.69-0.89)</td><td><0.001</td></tr>
</table>

<table>
<tr><th>Stent Thrombosis, N (%)</th><th>TCG n=5640</th><th>CLP n=5649</th><th>HR (95% CI)</th><th>p-value</th></tr>
<tr><td>Definite</td><td>71 (1.3)</td><td>106 (1.9)</td><td>0.67 (0.50-0.91)</td><td>0.009</td></tr>
<tr><td>Probable or definite</td><td>118 (2.2)</td><td>158 (2.9)</td><td>0.75 (0.59-0.95)</td><td>0.02</td></tr>
<tr><td>Possible, probable, or definite</td><td>155 (2.9)</td><td>202 (3.8)</td><td>0.77 (0.62-0.95)</td><td>0.01</td></tr>
</table>

<table>
<tr><th>Safety Endpoints</th><th>TCG n=9235</th><th>CLP n=9186</th><th>HR (95% CI)</th><th>p-value</th></tr>
</table>
</td>
</tr>
</table>

other reason that study drug should not be administered
- Oral anticoagulation therapy that cannot be stopped
- Fibrinolytic therapy planned or within the previous 24 hours
- Concomitant oral or IV therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers
- Index event is an acute complication of PCI
- PCI after index event and before first study dose
- Increased risk of bradycardic events
- Dialysis required
- Known clinically important thrombocytopenia or anemia
- Any other condition that may put the patient at risk or influence study results

Primary Bleeding Endpoints , n (%)				
Major bleeding, PLATO Criteria	961 (11.6)	929 (11.2)	1.04 (0.95-1.13)	0.43
Major bleeding, TIMI criteria	657 (7.9)	638 (7.7)	1.03 (0.93-1.15)	0.57
Life-threatening or fatal bleeding, PLATO criteria	491 (5.8)	480 (5.8)	1.03 (0.90-1.16)	0.70
Fatal bleeding	20 (0.3)	23 (0.3)	0.87 (0.48-1.59)	0.66
Intracranial bleeding	26 (0.3)	14 (0.2)	1.87 (0.98-3.58)	0.06
Fatal	11 (0.1)	1 (0.01)	—	0.02
Nonfatal	15 (0.2)	13 (0.2)	—	0.69
Secondary Bleeding Endpoints, n (%)				
Non-CABG-related Major Bleeding,				
PLATO criteria	362 (4.5)	306 (3.8)	1.19 (1.02-1.38)	0.03
TIMI criteria	221 (2.8)	177 (2.2)	1.25 (1.03-1.53)	0.03
CABG-related Major Bleeding				
PLATO criteria	619 (7.4)	654 (7.9)	0.95 (0.85-1.06)	0.32
TIMI criteria	446 (5.3)	476 (5.8)	0.94 (0.82-1.07)	0.32
Major or Minor Bleeding				
PLATO criteria	1339 (16.1)	1215 (14.6)	1.11 (1.03-1.20)	0.008
TIMI criteria	946 (11.4)	906 (10.9)	1.05 (0.96-1.55)	0.33

Other Safety Results, n (%)	**TCG**	**CLP**	**p-value**
Dyspnea	1270 (13.8%)	721 (7.8%)	< 0.001
D/C due to dyspnea	79 (0.9%)	13 (0.1%)	< 0.001
Bradycardia	409 (4.4%)	372 (4.0%)	0.21
Ventricular Pauses, Week 1			
≥3 seconds	84 (5.8%)	51 (3.6%)	0.01
≥5 second	29 (2.0%)	17 (1.2%)	0.10
Ventricular Pauses, 30 days			
≥3 seconds	21 (2.1%)	17 (1.7%)	0.52
≥5 seconds	8 (0.8%)	6 (0.6%)	0.60

Laboratory Safety Results, mean ± SD	TCG	CLP	p-value
Serum Uric Acid: % Increase From Baseline			
At 1 month	14±46	± 4	<0.001
At 12 months	15±52	7±31	< 0.001
1 month after D/C	7±43	8±48	0.56
Serum Creatinine: % Increase From Baseline			
At 1 month	10±22	8±21	<0.001
At 12 months	11±22	9±22	<0.001
1 month after D/C	10±22	10±22	0.59

Treatment-by-region interaction in PLATO Mahaffey et al. *Circulation*. 2011;124:544-554. Mahaffey et al. Data supplement. *Circulation*. 2011. Available at: http://circ.ahajournals.org/content/early/2011/06/27/CIRCULATIONAHA.111.047498/rel-suppl/38733e1ac2b68d61/suppl/DC1. Accessed July 20, 2011.	**In PLATO, r**esults in the ROW compared to effects in North America (US and Canada) showed a smaller effect in North America, numerically inferior to the control and driven by the US subset. **Aim:** To analyze potential explanations for the regional interaction observed in the PLATO study.	Treatment for the main PLATO study	Iinclusion and exclusion criteria for the main PLATO study	**Primary Efficacy:** • Time to first occurrence of any event from the composite of death from vascular causes, MI, or stroke **Secondary Efficacy:** • Composite of death from any cause, MI, or stroke • Composite of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event • MI • Death from CV causes • Stroke • Death from any cause **Primary Safety:** • Time to first occurrence of any major bleeding event **Secondary Safety:** • Minor bleeding • Dyspnea • Arrhythmia • Ventricular pauses • Unanticipated AEs • Laboratory safety results	• Data for TCG were consistent with the overall study population in all but 3 subgroups. The benefit of TCG appeared to be attenuated in patients with body weight below the median for their sex (p=0.04 for the interaction); in patients not taking lipid-lowering drugs at randomization (p=0.04 for the interaction), and in patients enrolled from North America (p=0.045 for the interaction). In North America, TCG did not result in a lower event rate compared to CLP. • Among the 37 multiple patient factors and concomitant therapies explored, investigators identified ASA maintenance dose as accounting for a substantial portion of the regional interaction. Results of the analyses by AstraZeneca using the median MD of ASA indicated that ASA MD could account for 80–100% of the observed regional interaction. The landmark approach using the ASA dose taken on Day 4 explained approximately 40% of the interaction effect. • Both analyses found that when given with low-dose ASA, TCG achieved lower event rates for the primary efficacy endpoint compared to CLP in the ROW and in the US. In an assessment of bleeding by region, no treatment-by-region interaction (p=0.9048) was observed for PLATO-defined major bleeding (US: 12.2% with TCG vs. 11.9% with CLP, p=0.7572; ROW: 11.5% with TCG vs. 11.1% with CLP, p=0.4696); therefore, the results were similar to those of the overall study.

PLATO substudy of medically managed ACS

James SK, et al. [published online ahead of print]. *BMJ*. 2011. http://www.bmj.com/content/342/bmj.d3527.full.pdf?sid=be2340bd-42ec-4ae1-8e63-58e1b2f453c7. Accessed July 20, 2011.

Prespecified analysis of a prerandomized subgroup of patients from PLATO who were intended for a noninvasive management strategy.

Aim: To compare the efficacy and safety of TCG vs. CLP in patients in PLATO with a planned noninvasive treatment at randomization

N=5216

Dosing was the same as that in the main PLATO study.

At baseline:

- Patients in the noninvasive cohort were older, more were women, and more had a history of heart disease versus patients in the invasive cohort.

At final diagnosis:

- Patients in the noninvasive cohort had a lower rate of STEMI and a higher incidence of NSTEMI and UA than those in the invasive cohort

Inclusion: Patients from the PLATO study that had a planned noninvasive strategy.Iinclusion was the same as those for the main PLATO study.

Exclusion: Exclusion criteria for were same for the main PLATO study.

Primary Efficacy Endpoint: Time to first occurrence of the composite of CV death from MI, or stroke.

Primary Safety Endpoint: Time to first occurrence of PLATO-defined major bleeding event.

- Despite the initial intent for noninvasive management, approximately 60% of patients (n=3143) were ultimately managed noninvasively.
- At the end of follow-up, 40% of patients (2040/5216) in the noninvasive cohort had undergone revascularization with 72.6% (1514/2040) having PCI only, 25.8% (559/2040) having CABG only, and 1.6% (33/2040) having both PCI and CABG.
- In the planned noninvasive cohort, TCG significantly reduced the incidence of the primary composite endpoint (CV death, MI, or stroke), all-cause mortality, and CV death versus CLP. The rate of stroke did not differ significantly between treatment groups.

Efficacy Endpoints in Patients With a Planned Noninvasive Treatment.[a,b]

	TCG n= 2601	CLP n= 2615	HR (95% CI)	p-value
Primary Endpoint				
CV death, MI (excluding silent), or stroke	295 (12.0)	346 (14.3)	0.85 (0.73-1.00)	0.045
Secondary Endpoints				
MI	176 (7.2)	187 (7.8)	0.94 (0.77-1.15)	0.555
CV death	132 (5.5)	173 (7.2)	0.76 (0.61-0.96)	0.019
All-cause mortality	147 (6.1)	195 (8.2)	0.75 (0.61-0.93)	0.010
NonCV death	15 (0.6)	22 (1.0)	0.68 (0.35-1.31)	0.252
Stroke	50 (2.1)	37 (1.7)	1.35 (0.89-2.07)	0.162
Ischemic	37 (1.5)	32 (1.4)	NR	0.530
Hemorrhagic	11 (0.5)	4 (0.2)	NR	0.069
Unknown	5 (0.2)	1 (0.06)	NR	0.124
CV death, MI, stroke, composite ischemic events,[c] or other arterial events	460 (18.6)	492 (20.3)	0.94 (0.82-1.06)	0.309

[a]Values are Kaplan-Meier estimates at 360 days; [b]Data are presented as n (%) unless otherwise noted; [c]Severe recurrent cardiac ischemia, recurrent cardiac ischemia,TIA.

Bleeding in Patients With a Planned Noninvasive Treatment (K-M estimates of n (%) at 12 mos).

	TCG n= 2601	CLP n= 2615	HR (95% CI)	p-value
Primary Safety Endpoint				
Total major bleeding	272 (11.9)	238 (10.3)	1.17 (0.98-1.39)	0.079
Life-threatening or fatal bleeding	125 (5.5)	129 (5.6)	0.99 (0.77-1.26)	0.911
Intracranial bleeding	11 (0.5)	4 (0.2)	2.83 (0.90-8.90)	0.075
Other major bleeding	154 (6.8)	114 (4.9)	1.38 (1.09-1.76)	0.009
Secondary Safety Endpoint—Major Bleeding Events				
Non-CABG-related	90 (4.0)	71 (3.1)	1.30 (0.95-1.77)	0.103
CABG-related	189 (8.3)	174 (7.5)	1.11 (0.90-1.36)	0.335
Coronary procedure-related	211 (9.2)	191 (8.2)	1.13 (0.93-1.37)	0.231
Noncoronary procedure-related	1 (0.04)	7 (0.4)	0.15 (0.02-1.19)	0.072
Secondary Safety Endpoint—Major or Minor Bleeding Events				
Total	378 (16.4)	332 (14.4)	1.17 (1.01-1.36)	0.0358
NonCABG-related	190 (8.3)	151 (6.7)	1.29 (1.04-1.60)	0.0182
CABG-related	202 (8.9)	196 (8.5)	1.05 (0.86-1.28)	0.6341
Coronary procedure-related	250 (10.8)	235 (10.0)	1.09 (0.91-1.30)	0.3657
Non-coronary procedure-related	11 (0.5)	16 (0.8)	0.70 (0.33-1.51)	0.3632
Other Safety Endpoints				
TIMI-defined Cutoff Point for Major Bleeding				
Total	181 (7.9)	164 (7.2)	1.13 (0.91-1.39)	0.270
NonCABG-related	61 (2.8)	47 (2.2)	1.33 (0.91-1.94)	0.142
CABG-related	124 (5.4)	122 (5.3)	1.03 (0.80-1.33)	0.799
Transfusion of Blood Products				
PRBCs	174 (7.6)	172 (7.2)	1.03 (0.83-1.27)	0.804
Platelets	30 (1.3)	27 (1.2)	1.13 (0.67-1.90)	0.645
FFP	55 (2.4)	50 (2.2)	1.12 (0.76-1.64)	0.565

<table>
<tr>
<td>PLATO invasive substudy

Cannon CP, et al. Lancet. 2010; 375:283-293.</td>
<td>Phase III multinational, randomized, double-blind, double-dummy, event-driven study conducted in 43 countries.

Aim: to compare the efficacy and safety of TCG with CLP in patients with ACS who were planned to undergo an invasive strategy (angiography, PCI, or CABG).</td>
<td>N=13,408

Dosing is summarized above in the PLATO main study.

Follow-up: 12 months.

Median exposure to study drug was 277 days (182-365) in the TCG group and 279 days (178-365) in the CLP group.</td>
<td>Inclusion: Patients from the PLATO study that had a planned invasive strategy.</td>
<td>Primary Endpoints:
• Composite of death from vascular causes, MI, or stroke
• PLATO-defined total major bleeding

Secondary Endpoints:
• Composite of all-cause mortality, MI, or stroke
• Death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event
• Components of the primary endpoint
• All-cause mortality
• Stent thrombosis</td>
<td>13,408 (72%) of the 18,624 patients randomized in PLATO were specified by the investigator as having the intent for invasive treatment strategy at the time of randomization.
<table>
<tr><th>Efficacy Endpoints, n (%)</th><th>TCG</th><th>CLP</th><th>HR (95% CI)</th><th>p-value</th></tr>
<tr><td>Primary</td><td>n=6732</td><td>n=6676</td><td></td><td></td></tr>
<tr><td>CV death, MI, stroke</td><td>569 (9.0%)</td><td>668 (10.7%)</td><td>0.84 (0.75-0.94)</td><td>0.0025</td></tr>
<tr><td>Secondary</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total death, MI, stroke</td><td>595 (9.4%)</td><td>701 (11.2%)</td><td>0.84 (0.75-0.94)</td><td>0.0016</td></tr>
<tr><td>CV death, MI, stroke, recurrent ischemia, TIA, arterial thrombotic event</td><td>830 (13.1%)</td><td>964 (15.3%)</td><td>0.85 (0.77-0.93)</td><td>0.0005</td></tr>
<tr><td>MI</td><td>328 (5.3%)</td><td>406 (6.6%)</td><td>0.80 (0.69-0.92)</td><td>0.0023</td></tr>
<tr><td>CV death</td><td>221 (3.4%)</td><td>269 (4.3%)</td><td>0.82 (0.68-0.98)</td><td>0.0250</td></tr>
<tr><td>Stroke</td><td>75 (1.2%)</td><td>69 (1.1%)</td><td>1.08 (0.78-1.50)</td><td>0.6460</td></tr>
<tr><td>Ischemic</td><td>59 (0.9%)</td><td>59 (0.9%)</td><td>—</td><td>1.0000</td></tr>
<tr><td>Hemorrhagic</td><td>12 (0.2%)</td><td>9 (0.1%)</td><td>—</td><td>0.6634</td></tr>
<tr><td>Unknown</td><td>5 (0.07)</td><td>1 (0.01%)</td><td>—</td><td>0.2187</td></tr>
<tr><td>All-cause mortality</td><td>252 (3.9%)</td><td>311 (5.0%)</td><td>0.81 (0.68-0.95)</td><td>0.0103</td></tr>
</table>
</td>
</tr>
</table>

Stent Thrombosis n (%)	TCG n=4949	CLP n=4928	HR (95% CI)	p-value
Definite	62 (1.3%)	97 (2.0%)	0.64 (0.46-0.88)	0.0054
With DES	17 (1.3%)	25 (1.8%)	0.69 (0.37-1.27)	0.2304
With BMS	45 (1.4%)	72 (2.1%)	0.62 (0.43-0.90)	0.0115
Probable or definite	104 (2.2%)	142 (3.0%)	0.73 (0.57-0.94)	0.0142
With DES	32 (2.3%)	36 (2.5%)	0.90 (0.56-1.45)	0.6581
With BMS	72 (2.2%)	106 (3.1%)	0.67 (0.50-0.91)	0.0092
Total	132 (2.8%)	179 (3.8%)	0.73 (0.59-0.92)	0.0068
With DES	41 (3.1%)	53 (3.8%)	0.78 (0.52-1.17)	0.2349
With BMS	91 (2.7%)	126 (3.8%)	0.71 (0.55-0.94)	0.0142

Safety (Bleeding) Endpoints	TCG n=6651	CLP n=6585	HR (95% CI)	p-value
Primary, n (%)				
Major , PLATO	689 (11.5%)	691 (11.6%)	0.99 (0.89-1.10)	0.8803
Life-threat-ening or fatal, PLATO	366 (6.0%)	351 (5.9%)	1.04 (0.90-1.20)	0.6095
Intracranial	15 (0.3%)	11 (0.2%)	1.36 (0.63-2.97)	0.4364
Other major	340 (5.9%)	360 (6.2%)	0.94 (0.81-1.09)	0.4030
Secondary, n (%)				
Non-CABG-related Major Bleeding				
PLATO criteria	272 (4.7%)	235 (4.0%)	1.16 (0.97-1.38)	0.1040
TIMI criteria	160 (2.8%)	130 (2.2%)	1.23 (0.98-1.55)	0.0814
CABG-related Major Bleeding				
PLATO criteria	430 (7.1%)	480 (8.0%)	0.89 (0.78-1.01)	0.0745
TIMI criteria	322 (5.3%)	354 (5.9%)	0.90 (0.78-1.05)	0.1914
Major Bleeding				
TIMI criteria	476 (7.9%)	474 (7.9%)	1.00 (0.88-1.14)	1.000

					Major or Minor Bleeding				
					PLATO criteria	961 (16.0%)	883 (14.7%)	1.09 (0.99-1.19)	0.0700
					TIMI criteria	675 (11.2%)	678 (11.3%)	0.99 (0.89-1.10)	0.8573

PLATO subanalysis of STE-ACS with PCI Steg PG, James S, Harrington RA, et al for the PLATO study group. *Circulation*. 2010;122:2131-2141.	Predefined subanalysis in the PLATO trial (described above) **Aim:** To evaluate the efficacy and safety of ticagrelor compared to clopidogrel in a subgroup of patients from PLATO with STE-ACS intended for reperfusion with primary PCI.	N=7544 patients presented with STE-ACS and an additional 886 patients had STEMI documented as a discharge diagnosis. Dosing is summarized above in the PLATO main study.	**Inclusion:** Same as those for the main PLATO study. Patients had either • Persistent STE ≥1 mV for ≥20 minutes (not known to be pre-existing or due to a coexisting disorder) in ≥2 contiguous leads and planned primary PCI within the first 24 hours of symptom onset or • New or presumed new LBBB and planned primary PCI. **Exclusion:** Same as those for PLATO overall	**Primary Efficacy Endpoint:** Time to first occurrence of the composite of CV death, MI, or stroke **Secondary Endpoints:** Time to first occurrence of • All-cause death, MI, and stroke • CV death, MI, stroke, ischemia, TIA, arterial thrombotic events • MI • Stroke • CV death • All-cause mortality **Stent Thrombosis Endpoints:** • Definite • Probable or definite • Possible, probable, or definite **Primary Safety Endpoint:** Time to first occurrence of any major bleeding event in the total cohort Sensitivity analyses were performed with different definitions of STEMI, including those patients with STEMI as a discharge diagnosis.	• Treatment groups were balanced with regards to baseline characteristics, initial treatments, and procedures. • Patients in the TCG group had a 13% lower relative risk for the occurrence of a primary efficacy endpoint compared to CLP-treated patients. • There was no significant interaction between the treatment effect and the presence or absence of STE/LBBB (interaction p-value: p=0.29). • The effect of TCG on the primary endpoint was consistent across the various predefined subgroups classified by prerandomization characteristics or postrandomization treatment use. For all regions other than North America, the HR for TCG versus CLP was <1 (p for interaction=0.39). • Using the sensitivity analysis, there was a similar effect on the primary endpoint for patients with STE-ACS at presentation, LBBB at presentation, and with a discharge diagnosis of STEMI. • The incidence of several secondary efficacy endpoints was reduced in the TCG group, including MI alone, total mortality, and definite stent thrombosis. • The number of strokes was low for both groups, with a higher rate with TCG (1.7% vs. 1.0%, p=0.02).

Major Efficacy Endpoints

Endpoints[a]	TCG n=3752	CLP n=3792	HR (95% CI)	p-value
Primary Endpoint, %				
CV, MI, stroke	9.4	10.8	0.87 (0.75-1.01)	0.07
Secondary Endpoints, %				
CV death and MI (excluding silent)	8.4	10.2	0.82 (0.71-0.96)	0.01
Total death, MI (excluding silent), stroke	9.8	11.3	0.87 (0.75-1.00)	0.05
CV death, MI (total), stroke, SRI, RI, TIA, arterial thrombotic events	13.3	15.0	0.87 (0.77-0.99)	0.03
MI (excluding silent)	4.7	5.8	0.80 (0.65-0.98)	0.03
CV death	4.5	5.5	0.83 (0.67-1.02)	0.07
Stroke	1.7	1.0	1.63 (1.07-2.48)	0.02
Nonhemorrhagic	1.2	0.8	1.58 (0.97-2.56)	0.06
Hemorrhagic	0.3	0.2	—[b]	—[b]
Unknown	0.1	0.0	—[b]	—[b]
Fatal stroke	0.37	0.16	2.36 (0.91-6.14)	0.08
All-cause mortality	5.0	6.1	0.82 (0.67-1.00)	0.05
Non-CV death	0.5	0.7	0.77 (0.40-1.48)	0.43
Stent Thrombosis Endpoints,[c] %				
Definite	1.6	2.4	0.66 (0.45-0.95)	0.03
Probable or definite	2.6	3.4	0.74 (0.55-1.00)	0.05
Possible, probable, or definite	3.3	4.3	0.75 (0.57-0.99)	0.04

[a] Percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than 1 type of endpoint. [b] HR and p-values are not reported when the total number of event <20. [c] Endpoints reported in patients that received at least 1 ste

Major Safety Endpoints

Endpoints[a]	TCG n= 3719	CLP n= 3752	HR (95% CI)	p-value

PLATO Bleeding Definition, %					
Major	9.0	9.2	0.98 (0.83-1.14)	0.76
Life-threatening	4.7	4.9	0.98 (0.79-1.22)	0.86
Non-CABG–related major	4.1	3.7	1.06 (0.84-1.35)	0.61
CABG-related major[b]	5.1	5.8	0.90 (0.73-1.10)	0.30
Other procedure-related major	1.7	1.8	0.96 (0.68-1.36)	0.83
Non-procedure–related major	2.6	2.0	1.19 (0.86-1.64)	0.30
Major and minor	13.1	12.3	1.05 (0.92-1.21)	0.43
Non-CABG–related major and minor	7.7	6.5	1.16 (0.97-1.38)	0.11
CABG-related major and minor	5.8	6.5	0.89 (0.73-1.09)	0.26
Other procedure-related major, minor	3.2	3.1	1.05 (0.81-1.36)	0.72
Nonprocedure–related major and minor	5.1	3.7	1.31 (1.04-1.66)	0.02
Minor (only) bleed	4.9	3.8	1.26 (1.00-1.59)	0.05
TIMI Definition, %[c]				
TIMI major	6.1	6.4	0.96 (0.79-1.16)	0.66
Non-CABG–related TIMI major	2.5	2.2	1.09 (0.80-1.48)	0.60
TIMI major and minor	8.8	8.9	0.97 (0.83-1.14)	0.72
Non-CABG–related TIMI major and minor	4.0	3.5	1.08 (0.85-1.38)	0.52
TIMI fatal/life-threatening	4.3	4.5	0.98 (0.78-1.23)	0.89
TIMI minor (only)	3.0	2.8	1.04 (0.79-1.38)	0.77
Fatal Bleeds, %	0.2	0.1	--[d]	--[d]
Fatal nonintracranial	0.1	0.1	--[d]	--[d]
Fatal intracranial	0.1	0.1	--[d]	--[d]

[a]Percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than 1 type of endpoint; [b]Percentages given are of the total number of patients; [c]TIMI bleeding rates were calculated, not adjudicated; [d]HR and p-values were not reported when the total number of events <20.

- Dyspnea occurred more frequently in the TCG group compared with the CLP group (12.6% vs. 8.4%; p<0.0001).

<table>
<tr>
<td>PLATO CABG substudy

Held et al. J Am Coll Cardiol. 2011;57:672-684.</td>
<td>Retrospective analysis of a nonrandomized subgroup of patients from the PLATO trial who underwent CABG surgery and therefore provides exploratory information only.

The statistical analysis was based on events occurring from the CABG procedure until the end of the study.

Aim: To evaluate the efficacy and safety of ticagrelor and clopidogrel in patients with ACS undergoing CABG surgery, as a postrandomization strategy</td>
<td>1899 patients in the PLATO trial underwent CABG surgery postrandomization

This analysis included 1261 patients who underwent CABG with last intake of study drug ≤7 days prior to surgery.

Dosing is summarized above in the main PLATO main described above.

It was recommended that TCG/placebo-CLP be withheld for 24-72 hours, and CLP/placebo-TCG be withheld for 5 days prior to CABG surgery. Study drugs were to be restarted immediately after surgery and prior to discharge.

Follow-up: 1,3,6,9, and 12 months after hospital admission and 1 month following D/C of study treatment</td>
<td>Inclusion and exclusion criteria were the same as those for the main PLATO study.</td>
<td>Primary Endpoints:
• Time from CABG to first occurrence of any event from the composite of death from vascular causes (CV death), MI, or stroke
• PLATO-defined major CABG-related bleeding

Secondary Endpoints:
• Components of the primary endpoint
• All-cause mortality
• CABG-related mortality
• Various bleeding analyses</td>
<td>Outcomes from CABG Substudy.
<table>
<tr><th>Endpoints</th><th>TCG [a] n= 629</th><th>CLP [a] n= 629</th><th>HR (95% CI)</th><th>p-value[b]</th></tr>
<tr><td colspan="5">Primary Endpoint, %</td></tr>
<tr><td>CV death, MI, and stroke</td><td>66 (10.6)</td><td>79 (13.1)</td><td>0.84 (0.60-1.16)</td><td>0.2862</td></tr>
<tr><td colspan="5">Secondary Endpoints, %</td></tr>
<tr><td>MI,excluding silent</td><td>37 (6.0)</td><td>35 (5.7)</td><td>1.06 (0.66-1.68)</td><td>0.8193</td></tr>
<tr><td>All-cause mortality</td><td>29 (4.7)</td><td>58 (9.7)</td><td>0.49 (0.32-0.77)</td><td>0.0018</td></tr>
<tr><td>CV death</td><td>25 (4.1)</td><td>47 (7.9)</td><td>0.52 (0.32-0.85)</td><td>0.0092</td></tr>
<tr><td>Non-CV death</td><td>4 (0.7)</td><td>11 (2.0)</td><td>0.35 (0.11-1.11)</td><td>0.0748</td></tr>
<tr><td>Stroke</td><td>13 (2.1)</td><td>11 (2.1)</td><td>1.17 (0.53-2.62)</td><td>0.6967</td></tr>
<tr><td>Hemorrhagic</td><td>0 (0)</td><td>1 (0.2)</td><td>NR</td><td>NR</td></tr>
<tr><td>Nonhemorrha-gic/unknown</td><td>13 (2.1)</td><td>10 (1.9)</td><td>1.29 (0.57-2.95)</td><td>0.5430</td></tr>
</table>
[a]K-M estimate of the rate of the endpoint at 12 months postCABG; [b]p-values were calculated by means of Cox regression analysis.

• A sensitivity analysis was performed using the total CABG population (n=1899), which included all CABG patients postrandomization, irrespective of timing of study drug intake. Results were consistent with the study population.</td>
</tr>
</table>

Bleeding Outcomes from CABG Substudy.

Bleeding Endpoint	TCG[a] n=632 n (%)	CLP[a] n=629 n (%)	OR / HR (95% CI)	p-value[b]
Major CABG-related bleeding[c]	513 (81.2)	504 (80.1)	1.07 (0.80-1.43)	0.6691
CABG-related life-threatening or fatal bleeding[c]	276 (43.7)	268 (42.6)	1.04 (0.83-1.31)	0.7330
Fatal CABG bleeding[c]	5 (0.8)	6 (1.0)	0.83 (0.20-3.28)	0.7730
CABG-related intracranial bleeding[c]	0 (0)	0 (0)	NR	NR
All intracranial bleeding postCABG	1 (0.2)	1 (0.2)	1.01 (0.06-16.09)	0.9967
CABG TIMI-defined all major bleeding[c]	375 (59.3)	362 (57.6)	1.08 (0.85-1.36)	0.5300
CABG TIMI-defined, minor bleeding[c]	133 (21.0)	136 (21.6)	0.97 (0.73-1.28)	0.8367
CABG-related GUSTO-defined severe bleeding[c]	67 (10.6)	77 (12.2)	0.85 (0.59-1.22)	0.3768

[a]For time-to-event outcomes, percent (%) is the K-M estimate of the rate of the endpoint at 12 months postCABG; [b]p-values are from Cox regression analysis (time-to-event outcomes) or Fisher's exact test (binary outcomes); [c]Binary outcome with OR.

PLATO substudy of CYP2C19 and ABCB1 polymorphisms Wallentin et al. *Lancet.* 2010;376:1320-1328.	Substudy of PLATO, a multicenter, double-blind, randomized study that compared TCG to CLP for the prevention of major CV events in patients with ACS treated with ASA. **Aim:** To investigate the role of CYP2C19 and ABCB1 polymorphisms on the efficacy and safety outcomes of the PLATO study	N=10,285 patients from whom a single blood sample was obtained **Treatment:** • TCG 180 mg x 1, then 90 mg BID, or • CLP 300 mg x 1, then 75 mg QD Patients received a LD of CLP if they had not been taking CLP or TCG for ≥5 days prior to randomization. Patients undergoing PCI: • Additional 90 mg of TCG if >24 hours after randomization. • Additional 300 mg of CLP at the discretion of the investigator, irrespective of the time in relation to randomization. ASA 75-100 mg QD unless intolerant. ASA 325 mg QD for ASA-naive patients and after stent placement (up to 6 months).	Same as those for the PLATO trial	*Primary Analyses:* TCG vs. CLP, stratified by genotype group, for the following outcomes: • primary efficacy composite of CV death, MI, or stroke • composite of CV death or MI • stent thrombosis • PLATO total major bleeding • PLATO non-CABG-related total major bleeding • PLATO CABG-related total major bleeding • composite of CV death, MI, stroke, and PLATO non-CABG-related major or PLATO CABG-related major fatal/life-threatening bleeding	• Occurrence of the primary endpoint of PLATO (composite of CV death, MI, or stroke) was lower with TCG compared to CLP. • A fewer number of events from the primary efficacy endpoint were seen with TCG than CLP in patients with any CYP2C19 LOF allele (p=0.0380). A similar trend was also observed in patients without CYP2C19 LOF allele (p=0.0608). In the TCG group, the rate of the primary efficacy endpoint was similar in patients with (8.6% per year) or without (8.8% per year) any LOF allele during the entire treatment period. • In the TCG group, no variation in bleeding rates in relation to CYP2C19 or ABCB1 polymorphisms was observed. Patients receiving CLP who had any CYP2C19 GOF allele had significantly higher rates of PLATO-defined major bleeding compared to those without any GOF or LOF alleles (p=0.022).

PLATO subanalysis of TCG in patients with CKD
 	
James et al. *Circulation*. 2010d;122:1056-1067.
	Substudy of PLATO, a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared TCG to CLP for the prevention of CV events in 18,624 patients with ACS.
	
	Aim: To compare the main efficacy and bleeding outcomes of TCG with those of CLP in relation to renal function of patients in PLATO
		N=15,202 patients in PLATO for whom SCr levels were available
		
		Randomization to either TCG or CLP:
		• TCG
		  ○ 180-mg LD followed by 90 mg twice daily.
		  ○ Patients undergoing PCI received an additional 90-mg dose if the procedure was more than 24 hours after randomization.
		• CLP
		  ○ 300-mg LD followed by 75 mg once daily.
		  ○ Patients undergoing PCI could receive an additional 300-mg LD at the discretion of the investigator.
		• Patients received ASA once daily unless intolerant.
			Key Inclusion Criteria:
			• Age ≥18 years
			• Hospitalization with documented evidence of ACS within 24 hours of randomization
			
			Key Exclusion Criterion: End-stage renal failure that required dialysis
				Primary Efficacy Endpoint: Time to first occurrence of the composite of CV death, MI, or stroke.
				
				Primary Safety Endpoint: Time to first occurrence of PLATO-defined major bleeding event
					• Twenty-one percent of the 15,202 patients with available SCr levels at baseline had CKD (ie, CrCL <60 mL/min).
					• In patients with CKD, the composite endpoint of CV death, MI, or stroke occurred significantly less often in the TCG group vs. the CLP group. The RRR was 23% for the composite endpoint of CV death, MI, or stroke, and 28% for total mortality.
					• Patients with CKD had an increased risk of bleeding.
					  ○ The incidence of PLATO-defined major bleeding was not significantly different between treatment groups in patients with normal renal function or in patients with CKD.
					  ○ The incidence of non-CABG major bleeding and intracranial bleeding was numerically higher with TCG, whereas the incidence of fatal bleeding was numerically higher with CLP.
					• The incidence of dyspnea was higher during treatment with TCG. SCr from baseline to 12 months was significantly higher with TCG compared to CLP, but was similar between groups 1 month after the end of treatment.

PLATO substudy of outcomes in patients with DM
 	
James et al. *Eur Heart J.* 2010a;31:3006-3016.
	Prespecified subgroup analysis of PLATO, a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared TCG to CLP for the prevention of CV events in 18,624 patients with ACS.
	
	Aim: To compare the effect of TCG with that of CLP on the outcomes of patients with DM or poor glycemic control
	
	Cohort with DM not powered to show difference in primary outcome between TCG and CLP treatment groups.
	
	There was no stratification based on DM status, DM type, or glycemic control before randomization.
		• Patients were randomized within 24 hours of ACS event to either TCG or CLP.
		  ○ TCG 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
		  ○ CLP 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of CLP at the discretion of the investigator.
		• Patients received ASA once daily unless intolerant.
			Same as those of the overall PLATO trial	**Primary Efficacy Endpoint:** Time to first occurrence of the composite of death from vascular causes, MI, or stroke.
				
				Primary Safety Endpoint: Time to first occurrence of PLATO-defined major bleeding event.
					Efficacy Results
					• Among patients with DM in the TCG group, the incidences of the efficacy endpoints (composite of CV death, MI, or stroke; all-cause mortality; or MI) were lower but not significantly different than those among diabetic patients in the CLP group.
					• Among patients with a HbA_{1c} concentration ≥6% (median value) and among those with a SG concentration ≥6.8 mmol/L (median value), patients treated with TCG had significantly greater reductions in the primary composite endpoint and all-cause mortality than did those treated with CLP.
					• Patients treated with insulin had greater rates of the primary composite endpoint and all-cause mortality than did diabetic patients who were not treated with insulin. Effects of TCG and CLP treatments were consistent with the overall trial results.
					
					Safety Results
					• Rates of major bleeding in the TCG and CLP groups, regardless of DM status, were similar and consistent with those of the overall study population. PLATO-defined, non-CABG–related bleeding events were numerically more common in the TCG-treated group of diabetic patients than in the CLP-treated group. CABG-related bleeding events were numerically more common in the CLP-treated group of diabetic patients than in the TCG-treated group.
					• Among patients receiving insulin before the index event, the rate of PLATO-defined major bleeding for those treated with TCG was similar to that of patients treated with clopidogrel. The incidence of PLATO-defined major bleeding was similar between treatment groups irrespective of insulin use and in patients with type II DM.

<table>
<tr>
<td>PLATO pulmonary substudy

Storey et al. Poster presented at: 59th Annual Scientific Session of the American College of Cardiology (ACC) held jointly with the ACC i2 Summit, March 14-16, 2010; Atlanta, Georgia. J Am Coll Cardiol. 2010c;55:E1007 (abstract A108).</td>
<td>Substudy of PLATO, a Phase III, international, randomized, double-blind, double-dummy, event-driven trial that compared TCG to CLP for the prevention of CV events in 18,624 patients with ACS.

Aim: To assess the effects of TCG vs. CLP on FEV_1 after completion of study treatment</td>
<td>N=199

Randomization to either TCG or CLP:
• TCG
○ 180-mg LD followed by 90 mg twice daily.
○ Patients undergoing PCI received an additional 90-mg dose if the procedure was more than 24 hours after randomization.
• CLP
○ 300-mg LD followed by 75 mg once daily.
○ Patients undergoing PCI could receive an additional 300-mg LD at the discretion of the investigator.

Patients received ASA once daily unless intolerant.

PFTs were performed after receiving 30-40 days of study medication, repeated within 10 days before the end of treatment, and repeated again 20-30 days after treatment D/C.</td>
<td>Key Inclusion Criteria:
Enrollment in the PLATO trial

Key Exclusion Criteria:
• Advanced lung disease
• Symptomatic heart failure
• Recent CABG surgery</td>
<td>Primary Endpoint:
FEV_1 after completion of study treatment</td>
<td>• Both groups had similar FEV_1 results at the different time points, with no apparent change over time or after discontinuation of study medication. Results of other PFT parameters also did not significantly differ between groups, with no apparent change over time or after discontinuation of study medication (shown in the following table).
• Six patients in the TCG group and 8 patients in the CLP group had an AE of dyspnea or event associated with dyspnea (eg, CHF or COPD exacerbation).

Effects of TCG and CLP on Pulmonary Function in Patients With ACS.[a,b]
<table>
<tr><th></th><th>TCG (n=101)</th><th>CLP (n=98)</th></tr>
<tr><td>FEV_1 pre-beta agonist (L)</td><td>2.81±0.73</td><td>2.70±0.84</td></tr>
<tr><td>FEV_1 post-beta agonist (L)</td><td>2.74±0.73</td><td>2.66±0.79</td></tr>
<tr><td>$FEF_{25\%-75\%}$ (%)</td><td>2.90±1.26</td><td>2.62±1.33</td></tr>
<tr><td>SpO_2 (%)</td><td>97±3</td><td>96±2</td></tr>
<tr><td>TLC (L)</td><td>6.42±1.28</td><td>6.27±1.36</td></tr>
<tr><td>FRC (L)</td><td>3.56±0.86</td><td>3.47±0.94</td></tr>
<tr><td>RV (L)</td><td>2.72±0.85</td><td>2.54±0.89</td></tr>
<tr><td>DLCO (%)</td><td>7.00±1.77</td><td>7.18±2.60</td></tr>
</table>
[a] Data are mean ± SD; [b] The p-values are nonsignificant for all parameters.</td>
</tr>
</table>

<table>
<tr>
<td>PLATO subanalysis of dyspnea and CV outcomes

Storey et al. [abstract and poster]. Poster presented at: European Society of Cardiology Congress 2010; August 28-September 1, 2010; Stockholm, Sweden. Eur Heart J. 2010d;31 (abstract suppl): 203. Abstract P1352.</td>
<td>Subanalysis of PLATO trial data from
• 9235 patients in the TCG group
• 9186 patients in the CLP group

Aim: To determine the incidence of dyspnea and its relationship with safety and efficacy outcomes</td>
<td>• Patients were randomized within 24 hours of ACS event to either
○ TCG 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose if the procedure was more than 24 hours after randomization.
○ CLP 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of CLP at the discretion of the investigator.
• Patients received ASA once daily unless intolerant.</td>
<td>Same as those of the overall PLATO trial</td>
<td>• Outcome evaluation was based on primary efficacy endpoint in PLATO (composite of death from vascular causes, MI, or stroke) and individual endpoints (MI, stroke, CV death, total morality).
• Incidence of PLATO-defined major and minor bleeding were evaluated.</td>
<td>• Dyspnea was reported as an AE for 1339 (14.5%) of patients in the TCG group and 798 (8.7%) of patients in the CLP group.
○ Fifteen percent of these dyspnea cases in the TCG group and 6.9% in the CLP group (p<0.0001) were considered related to the study drug.
○ Severe dyspnea occurred in 39 (0.4%) of TCG-treated patients and in 24 (0.3%) of CLP -treated patients.
○ Discontinuation of study medication due to dyspnea occurred for 79 (5.9%) in the TCG group with dyspnea and for 13 (1.6%; p<0.0001) in the clopidogrel group with dyspnea.
○ Ongoing dyspnea at the end of the study was reported for 5.0% of TCG-treated patients and for 3.1% of CLP -treated patients (p<0.0001).
• Patients with dyspnea in either treatment group were more likely than those without dyspnea to have a greater waist circumference, be older, and/or have a history of smoking, dyspnea, asthma, COPD, or chronic renal disease.
• The median time to dyspnea onset (on and off treatment) was significantly earlier in patients treated with TCG than in those treated with CLP (23 vs. 43 days; p<0.0001).
• The 12-month efficacy and safety outcomes of patients with dyspnea were compared with those of patients without dyspnea.
○ K-M incidences of the primary composite endpoint and MI at 12 months were significantly greater in those with dyspnea than in those without dyspnea in either treatment group.
○ No significant effect on stroke, CV death, or total mortality was identified for patients who reported dyspnea in either treatment group.
○ Major bleeding was significantly more common in those with dyspnea than in those without dyspnea in the TCG treatment group (p=0.033). Major or minor bleeding occurred significantly more often in patients with dyspnea than in those without this AE in either treatment group (p≤0.002).
• Twelve-month K-M rates of key efficacy endpoints for patients with dyspnea in the TCG group and CLP group are shown in the table.

<table>
<tr><th></th><th colspan="2">12-Month K-M Rate (%)</th><th></th></tr>
<tr><th>Endpoint</th><th>TCG</th><th>CLP</th><th>p-value</th></tr>
<tr><td>Primary composite</td><td>11.9</td><td>15.7</td><td>0.02</td></tr>
<tr><td>MI</td><td>8.7</td><td>11.3</td><td>0.09</td></tr>
<tr><td>CV death</td><td>3.3</td><td>4.8</td><td>0.035</td></tr>
</table>
• Compared with patients who experienced dyspnea within 30 days after randomization to CLP, those randomized to TCG had significantly lower incidences of CV death and total mortality from Day 31 through Day 360.</td>
</tr>
</table>

<table>
<tr>
<td>PLATO elderly substudy

Husted et al. [abstract and poster] Presented at: 60th Annual Scientific Session of the American College of Cardiology; April 2-5, 2011; New Orleans, LA. J Am Coll Cardiol. 2011; 57(14 suppl 1):E1099. Abs 1139-309.</td>
<td>Prespecified secondary subgroup analysis of PLATO, a Phase III, multinational, randomized, double-blind, double-dummy, parallel-group, event-driven study that compared TCG to CLP for the prevention of CV events in 18,624 patients with ACS.

Aim: To assess clinical outcomes in elderly (≥75 years) versus younger (<75 years) patients treated with TCG or CLP.

Elderly cohort not powered to show difference in primary outcome between TCG and CLP treatment groups.</td>
<td>• Patients were randomized within 24 hours of ACS event to either TCG or CLP.
○ TCG 180 mg LD followed by 90 mg twice daily. Patients undergoing PCI received an additional 90 mg dose of TCG if the procedure was more than 24 hours after randomization.
○ CLP 300 mg LD followed by 75 mg once daily. Patients undergoing PCI could receive an additional 300 mg LD of CLP at the discretion of the investigator.
• Patients received ASA once daily unless intolerant.</td>
<td>Same as those of the overall PLATO trial</td>
<td>Primary Efficacy Endpoint:
Time to first occurrence of the composite of death from vascular causes, MI, or stroke.

Primary Safety Endpoint:
Time to first occurrence of PLATO-defined major bleeding event.</td>
<td>Major Efficacy Results
In the overall PLATO study population, 9.8% of TCG-treated patients versus 11.7% of CLP-treated patients experienced an event from the composite primary endpoint (HR: 0.84; 95% CI: 0.77-0.92; p<0.001) at 12 months.
• When considering the ≥75 years and <75 years patient groups, this treatment effect was independent of age (interaction p-value of 0.22).
• For the secondary efficacy endpoints (all-cause mortality, MI, CV death, definite stent thrombosis), the treatment effect was independent of age (<75 vs. ≥75 years; p-value interaction was nonsignificant).

<table>
<tr><th></th><th></th><th colspan="2">K-M% at Month 12</th><th></th><th></th></tr>
<tr><th>Endpoint</th><th>Total Pts</th><th>TCG n= 9333</th><th>CLP n= 9291</th><th>HR (95% CI)</th><th>p-value (inter-action)</th></tr>
<tr><td colspan="6">CV death/MI/Stroke</td></tr>
<tr><td>≥75 yrs</td><td>471</td><td>17.2</td><td>18.3</td><td>0.94 (0.78-1.13)</td><td rowspan="2">0.22</td></tr>
<tr><td><75 yrs</td><td>1399</td><td>8.6</td><td>10.4</td><td>0.82 (0.74-0.91)</td></tr>
<tr><td colspan="6">All-cause Mortality</td></tr>
<tr><td>≥75 yrs</td><td>293</td><td>9.8</td><td>12.4</td><td>0.81 (0.65-1.03)</td><td rowspan="2">0.78</td></tr>
<tr><td><75 yrs</td><td>608</td><td>3.6</td><td>4.8</td><td>0.78 (0.67-0.92)</td></tr>
<tr><td colspan="6">MI</td></tr>
<tr><td>≥75 yrs</td><td>241</td><td>9.3</td><td>9.4</td><td>0.96 (0.75-1.24)</td><td rowspan="2">0.2</td></tr>
<tr><td><75 yrs</td><td>864</td><td>5.4</td><td>6.6</td><td>0.81 (0.71-0.93)</td></tr>
<tr><td colspan="6">CV Death</td></tr>
<tr><td>≥75 yrs</td><td>242</td><td>8.1</td><td>10.3</td><td>0.79 (0.61-1.02)</td><td rowspan="2">0.90</td></tr>
<tr><td><75 yrs</td><td>549</td><td>3.3</td><td>4.2</td><td>0.81 (0.68-0 95</td></tr>
<tr><td colspan="6">Definite Stent Thrombosis</td></tr>
<tr><td>≥75 yrs</td><td>25</td><td>1.8</td><td>2.1</td><td>0.66 (0.30-1.45)</td><td rowspan="2">0.94</td></tr>
<tr><td><75 yrs</td><td>141</td><td>1.3</td><td>1.9</td><td>0.67 (0.49-0.93)</td></tr>
</table>

Major Safety Results</td>
</tr>
</table>

In the overall PLATO study population, the occurrence of major bleeding was similar between TCG and CLP treatment groups when analyzed according to the PLATO bleeding criteria (11.6% vs. 11.2%, respectively; HR: 1.04, 95% CI: 0.95-1.13, p=0.43). PLATO-defined major bleeding was similar in both treatment groups and was independent of age (<75 vs. ≥75 years; interaction p-value of 1.00) as shown in the following table.

	Planned Invasive Management n=13,408			Planned Medical Management n=5216			
	K-M%		HR	K-M %		HR	p-value inter-action
	TCG	CLP	(95% CI)	TCG	CLP	(95% CI)	
CV Death, MI, Stroke Efficacy							
≥75 years	16.6	15.4	1.09 (0.85-1.38)	17.9	23.0	0.77 (0.59-1.01)	0.0360
<75 years	7.9	9.9	0.80 (0.70-0.90)	10.5	12.0	0.89 (0.74-1.08)	
All-cause Death							
≥75 years	9.3	10.3	0.95 (0.70-1.29)	10.6	15.8	0.67 (0.47-0.94)	0.1647
<75 years	3.2	4.3	0.77 (0.63-0.94)	4.9	6.2	0.81 (0.62-1.07)	
Major Bleeding							
≥75 years	16.6	16.0	1.03 (0.80-1.32)	10.6	9.4	1.11 (0.74-1.67)	0.7143
<75 years	10.8	10.9	0.99 (0.88-1.12)	12.2	10.5	1.18 (0.98-1.43)	
NonCABG-related Major Bleeding							
≥75 years	10.4	8.7	1.20 (0.86-1.67)	5.2	4 5	1.12 (0.62-2.02)	0.5753
<75 years	3.9	3.3	1.17 (0.96-1.44)	3.7	2.9	1.37 (0.95-1.98)	

- Dyspnea was observed more frequently in TCG-treated vs. CLP-treated patients. This observation did not differ between age groups.
- In the first week after randomization, but not at 30 days, ventricular pauses were recorded more frequently in the TCG group vs. the CLP group, with no difference between age groups.

Dyspnea and Ventricular Pauses by Age and Treatment.

	K-M %			
	TCG n=9333	**CLP n=9291**	**HR/OR[a] (95% CI)**	**p-value (inter-action)**
Dyspnea				
≥75 yrs	18.8	12.2	1.63 (91.33-1.90)	0.2072
<75 years	14.2	7.8	1.89 (1.70-2.09)	
Ventricular Pauses – First Week[b]				
≥3 seconds				
≥75 years	7.2	6.9	1.06 (0.54-2.08	0.1408
<75 years	5.5	2.9	1.92 (1.26-2.93)	
≥5 seconds				
≥75 years	2.8	2.7	1.05 (0.36-3.05)	0.2846
<75 years	1.8	0.9	2.14 (1.01-4.55)	
Ventricular Pauses – At 30 Days[c]				
≥3 seconds				
≥75 years	2.4	3.4	0.70 (0.20-2.54)	0.2907
<75 years	2.1	1.3	1.57 (0.73-3.38)	
≥5 seconds				
≥75 years	0.0	1.1	NR	NR
<75 years	1.0	0.5	2.03 (0.61-6.77)	

PLATO arrhythmia substudy

Scirica et al. *J Am Coll Cardiol.* 2011;57:1908-1916.

Prospective analysis of a subgroup of patients who had cECG monitoring in PLATO.

Aim: To perform cECG monitoring in a subset of patients from PLATO to determine whether TCG increased the risk of ventricular pauses and whether these pauses were associated with any clinical bradycardic events

N=2908 with cECG monitoring

- n=2866 (98.5%) had 1 week recordings
- n=1991 (68.4%) had 1 month recordings
- n=1949 (67%) had recordings at both 1 week and 1 month.

Median duration of cECG monitoring was

- 6.2 days during Week 1
- 6.8 days at Month 1.

Treatment:

- TCG
  - 180 mg LD and 90 mg BID thereafter
  - Additional 90 mg LD given if PCI occurred more than 24 hrs after randomization
- CLP
  - 300 mg LD if CLP-naive and 75 mg daily thereafter
  - Additional 300 mg LD for PCI (given at the discretion of the investigator)
- All received 75-100 mg ASA daily unless they were intolerant.

Same as those of the overall PLATO trial

cECG Arrhythmia Endpoints

- **Principal endpoint:** Incidence of ventricular pauses ≥3 seconds which was chosen on the basis of guidelines which recommend consideration of pacemaker placement in symptomatic patients with evidence of 3 second pauses
- **Other endpoints:** Incidence of
  - Ventricular pauses lasting at least 5 seconds
  - VT and SVT (any episode at >100 beats/min lasting at least 4 beats)
  - Other bradyarrhythmias such as sinus bradycardia (at least 4 beats ≤45 beats/min) or dropped beats (no ventricular beat within 180% of the previous RR interval).

Clinical Arrhythmia Endpoints

- AEs that could be related to bradycardic events based on prespecified, preferred AE terms
- Investigator-reported symptomatic events that were possibly bradycardic
- Information about the suspected etiology of syncope AEs and reasons for pacemaker insertion

- There was a significantly higher incidence of ventricular pauses ≥3 seconds in the first week in the TCG group compared with the CLP group as noted in the following table. At 1 month, pauses ≥3 s were reported less frequently, and the rate was similar between treatment groups.
- Most events were ventricular pauses of sinoatrial origin and considered asymptomatic and transient in nature. There was a peak in the frequency of ventricular pauses at night in the TCG group that was less evident in the CLP group.
- There was no difference between TCG and CLP in the incidence of clinically reported bradycardic AEs, including syncope, pacemaker placement, and cardiac arrest (see table below).

Arrhythmias at Visits 1 and 2.[a,b]

Characteristic	Visit 1 (Week 1)		
	TCG 90 mg BID (n=1451)	CLP 75 mg QD (n=1415)	RR (95% CI)
Heart rate (beats/min)	68.6±10.70	68.5±10.43	NA
Patients with ≥1 bradyarrhythmia[c]	812 (56.0)	737 (52.1)	1.07[d] (1.00-1.15)
Ventricular pauses ≥3 s	84 (5.8)	51 (3.6)	1.61[f] (1.14-2.26)
AV node pause	20 (1.4)	17 (1.2)	1.15 (0.60-2.18)
SA node pause	63 (4.3)	31 (2.2)	1.98 (1.30-3.03)
Other pause	7 (0.5)	7 (0.5)	0.98 (0.34- 2.77)
Ventricular pauses ≥5 s	29 (2.0)	17 (1.2)	1.66 (0.92-3.01)
AV node pauses	9 (0.6)	9 (0.6)	0.98 (0.39-2.45)
SA node pause	22 (1.5)	7 (0.5)	3.06[g] (1.31-7.15
Other pause	0	3 (0.2)	NR
Dropped beats	452 (31.2)	416 (29.4)	1.06 (0.95-1.18)
Bradycardia	575 (39.6)	535 (37.8)	1.05 (0.96-1.15)
Patients with ≥1 tachyarrhythmia	1014 (69.9)	961 (67.9)	1.03 (0.98-1.08)
Supraventricular tachyarrhythmia	844 (58.2)	781 (55.2)	1.05 (0.99-1.12)
Ventricular tachyarrhythmia	522 (36.0)	503 (35.5)	1.01 (0.92-1.12)

Characteristic	Visit 2 (Week 30)		
	TCG 90 mg BID n=1451	CLP 75 mg QD n=1415	RR (95% CI)
Heart rate (beats/min)	68.1±10.16	67.9±10.17	NA
Patients with ≥1 bradyarrhythmia[c]	565 (57.4)	506 (50.3)	1.14[e] (1.05-1.24)
Ventricular pauses ≥3 s	21 (2.1)	17 (1.7)	1.26 (0.67-2.38)
AV node pause	6 (0.6)	8 (0.8)	0.77 (0.27-2.20)
SA node pause	17 (1.7)	11 (1.1)	1.58 (0.74-3.35)
Other pause	0	0	NR
Ventricular pauses ≥5 s	8 (0.8)	6 (0.6)	1.36 (0.47-3.91)
AV node pauses	2 (0.2)	2 (0.2)	1.02 (0.14-7.24)
SA node pause	7 (0.7)	4 (0.4)	1.79 (0.52-6.09)
Other pause	0	0	NR
Dropped beats	292 (29.6)	266 (26.4)	1.12 (0.97-1.29)
Bradycardia	409 (41.5)	378 (37.6)	1.11 (0.99-1.23)
Patients with ≥1 tachyarrhythmia	605 (61.4)	623 (61.9)	0.99 (0.93-1.06)
Supraventricular tachyarrhythmia	528 (53.6)	551 (54.8)	0.98 (0.90-1.06)
Ventricular tachyarrhythmi	211 (21.4)	217 (21.6)	0.99 (0.84-1.17)

[a]Data are expressed as n (%) or mean ± standard deviation. [b]p values as noted below, all other p values are >0.05; [c]pause, dropped beat or episode of bradycardia; [d]p=0.04; [e] p=0.002; [f]p=0.006; [g]p=0.008.

AEs of Interest by Ventricular Pause Duration.

AE n (%)	All Patients		Patients With Ventricular Pauses ≥3 s		Patients With Ventricular Pauses ≥5 s	
	TCG n= 1472	CLP n= 1436	TCG n=89	CLP n=62	TCG n=32	CLP n=20
Patients with ≥1 AE of interest[a]	148 (10.1)	126 (8.8)	23 (25.8)	16 (25.8)	10 (31.3)	8 (40.0)
Dizziness	38 (2.6)	41 (2.9)	1 (1.1)	2 (3.2)	0	1 (5.0)
Hypotension	51 (3.5)	37 (2.6)	3 (3.4)	5 (8.1)	1 (3.1)	2 (10.0)
Bradycardia	61 (4.1)	36 (2.5)	16 (18.0)	7 (11.3)	7 (21.9)	4 (20.0)
Syncope	5 (0.3)	2 (0.1)	1 (1.1)	1 (1.6)	1 (3.1)	1 (5.0)
Cardiac arrest	3 (0.2)	6 (0.4)	2 (2.2)	2 (3.2)	1 (3.1)	1 (5.0)
Heart block	6 (0.4)	15 (1.0)	3 (3.4)	5 (8.1)	1 (3.1)	1 (5.0)
Loss of conscious-ness	0	2 (0.1)	0	0	0	0
Pacemaker placement[b]	7 (0.5)	14 (1.0)	5 (5.6)	5 (8.1)	3 (9.4)	2 (10)
Presyncope	0	0	0	0	0	0
Vasovagal syncope	3 (0.2)	1 (0.1)	0	0	0	0

AE = adverse event; s = second. [a] Patients could report in more than 1 AE category; [b]Patients could be counted in both temporary and permanent pacemaker placement categories, but each patient was counted only once for "pacemaker placement." Pacemaker placement included not only those pacemakers reported as AEs but also those recorded as a bradycardic events.

Phase II Studies					
Efficacy and Safety Data					

DISPERSE-2
 	
Cannon et al. *J Am Coll Cardiol*. 2007;50:1844-1851.
	Phase II randomized, double-blind, double-dummy trial conducted in the US and Europe.
	
	Aim: to assess the safety, tolerability, and initial efficacy of TCG, also known as AZD6140, compared with CLP in patients with NSTE-ACS.
		N=990
		
		TCG 90 mg BID or 180 mg BID
		
		Or
		
		CLP 300 mg LD, then 75 mg QD
		
		Treatment continued for 1, 2, or 3 months.
		
		Patients in the TCG group were further randomized to receive or not receive an initial 270 mg LD.
		
		Patients undergoing PCI within 48 hours post-randomization could be given an additional 300-mg LD of CLP (or placebo) at the discretion of the treating physician.
		
		All patients received ASA 325 mg x 1, followed by 75 to 100 mg QD.
			Inclusion:
			• Age ≥18 years
			• Hospitalized for NSTE-ACS in past 48 hrs
			• Ischemic symptoms at rest ≥10 min
			• Biochemical marker evidence of MI or ECG evidence of ischemia
			
			Exclusion:
			• Persistent ST-segment elevation ≥20 min, more than 48 h from onset of symptoms
			• Index event due to PCI within the prior 48 h or PCI within prior 48 h
			• Angiography showing no significant coronary stenosis
			• Conditions associated with increased risk of bleeding
			• CABG in prior 3 months
			• Nonhemorrhagic stroke within the prior 30 days
			• Active cancer (excluding skin basal cell carcinoma),
			• Oral anticoagulation therapy
			• Chronic non-selective NSAID use
			• Thrombolytic therapy within the prior 7 days
			• Contraindication to ASA
			• Concomitant therapy with digoxin or strong CYP450 3A4 inhibitors or CYP450 3A4 substrates with a narrow therapeutic index
			• SCr >3.0 mg/dL
			• Active liver disease or elevated liver function tests
			• Hb <10 g/dL
			• PLT <100 × 10^9/L
				Primary:
				• Evaluate total bleeding events in patients with NSTE-ACS within the first 4 weeks of treatment with TCG+ASA vs. CLP+ASA
				
				Secondary:
				• Individual and composite incidence of MI (including silent MI), death, stroke, and severe recurrent ischemia
				• Incidence of recurrent ischemia 4-7 days after randomization (Holter monitor)
					Primary Endpoint:
					• Over 4 weeks, protocol-defined major or minor bleeding occurred in 26 patients (8.1%) in the CLP group, 32 (9.8%) in the TCG 90 mg BID group, and 25 (8.0%) in the TCG 180 mg BID group (p=0.43 and p=0.96, respectively, vs. CLP).
					• The rates of major bleeding events (major-fatal/life-threatening and major-other) were not different between groups.
					• There were 2 fatal bleeds, both in the TCG 90 mg BID group.
					• Over 4 weeks, protocol-defined minor bleeding occurred in 4 patients (1.3%) in the CLP group, 9 (2.7%) in the TCG 90 mg BID group, and 12 (3.8%) in the TCG 180 mg BID group (p=0.18 and p=0.05 vs. CLP, respectively).
					• The most common type of bleeding was epistaxis, followed by periprocedural hemorrhage or hematoma.73% of all bleeds in the CLP group were periprocedural compared to 53% and 52% of bleeds in the TCG 90 and 180 mg groups, respectively.
					• Study discontinuation due to bleeding occurred in 3 (0.9%) in the CLP group, 8 (2.4%) in the TCG 90 mg group, and 5 (1.5%) in the TCG 180 mg group.
					
					Secondary Endpoints:
					• Over 12 weeks, protocol-defined major and minor bleeding was not different between CLP and TCG groups, with the exception of minor bleeding in the TCG 180 mg group (CLP: 4 [1.3%]; TCG 180 mg: 16 [6.1%], p=0.01).
					• Rates of death and CV death among treatment groups were not different.
					• Nonsignificant trend toward lower rates of MI in the TCG groups (CLP: 15 [5.6%]; TCG 90 mg: 12 [3.8%]; TCG 180 mg: 8 [2.5%]).
					• K-M event rates of CV death, MI, or stroke were not different between CLP and TCG 90 mg and 180 mg (6.2%, 6.0%, and 3.5%, respectively).
					• Rates of nausea, dyspepsia, and hypotension were higher in TCG groups.
					• Dyspnea was reported in 21 patients (6.4%) in the CLP group, 35 (10.5%) in the TCG 90 mg BID group (p=0.07 vs. CLP), and 51 (15.8%) in the TCG 180 mg BID group (p<0.0002 vs. CLP).
					  ○ Dyspnea resolved within 24 hours in 27% of patients reporting this symptom, after 24 hours in 25% of patients, and persisted for >15 days in 48% of patients.
					  ○ The overall incidence of persistent dyspnea was 2% for CLP and 6% in both TCG groups.
					
					• Rates of ventricular tachycardias were not different in all treatment groups.
					• A greater number of mostly asymptomatic ventricular pauses lasting

					>2.5 seconds(s) were detected post hoc in TCG groups compared to the CLP group. • In patients with pauses >5 seconds, 7 were due to sinus block or sinus node exit block and 4 were due to complete heart block.

ACS = acute coronary syndrome; AEs = adverse events; ASA = aspirin; BMS = bare metal stent; CABG = coronary artery by-pass graft; CAD = coronary artery disease; CI = confidence interval; CLP = clopidogrel; CV = cardiovascular; D/C: discontinuation; DES = drug-eluting stent; ECGs = electrocardiograms; FFP = fresh frozen plasma; GOF = gain of function; GUSTO = Global Strategies for Opening Occluded Coronary Arteries; Hb = hemoglobin; HR = hazard ratio; IQR = interquartile range; K-M = Kaplan-Meier; LBBB = left bundle brach block; LD = loading dose; LOF = loss of function; MI = myocardial infarction; NR = not reported; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; NSTE = non-ST-segment elevation; NSTEMI = non-ST elevation myocardial infarction; OR = odds ration; PCI = percutaneous coronary intervention; PLATO = a study of PLATelet inhibition and patient Outcomes; PLT = platelets; RI= recurrent cardiac ischemia; ROW = rest of the world; RRR = relative risk reduction; SCr = serum creatinine; SD = standard deviation; SRI = severe recurrent cardiac ischemia; STE = ST-segment elevation; STEMI = ST-elevation myocardial infarction; TCG = ticagrelor; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; UA = unstable angina; US = United States

3.1.3.2 Published and Unpublished Studies for Off-Label Indications

TABLE 3-51: Summary Table of Key Studies for Off-Label Indications of Ticagrelor (BRILINTA)

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
Phase II Studies					
Pharmacokinetic and Pharmacodynamic Data					

DISPERSE
Husted et al. *Eur Heart J*. 2006;27:1038-1047
	Phase II multicenter, randomized, double-blind, double-dummy, parallel-group study conducted in Denmark, Hungary, and Norway.
	Aim: to assess the PK, PD, and safety of TCG (AZD6140) in patients with stable CAD treated with ASA.
		N = 200
		28 days of:
		TCG:
		• 50 mg BID (n=41),
		• 100 mg BID (n=39),
		• 200 mg BID (n=37), or
		• 400 mg QD (n=46)
		or
		CLP:
		• 75 mg QD (n=37)
		All patients received ASA 75-100 mg QD.
			Inclusion:
			• Confirmed atherosclerotic disease
			• ASA 75-100 mg ≥2 weeks before randomization
			• Men and post-menopausal or sterile women 25-85 years of age
			Exclusion:
			• ACS 3 months before randomization
			• PCI with balloon or stent 4 months before randomization
			• Conditions with ↑ risk of bleeding
			• SCr ≥1.2× ULN
			• Hb ≥5% below LLN
			• PLT <125 × 10^9/L
			• Active liver disease
			• Anticoagulation therapy 10 days before randomization
			• Antiplatelet therapy other than ASA 7 days before randomization
				PD Endpoints:
				• ADP-induced IPA
				  ○ Final extent
				  ○ Maximal extent
				• Collagen-induced IPA
				• Bleeding time
				PK Endpoints:
				• AUC
				• C_{max}
				• t_{max}
				• $t_{½}$
				• CL/F
				Safety Endpoints:
				• Incidence of AEs
				• Major bleeding
				• Minor bleeding
				• 12-lead ECGs
				• Laboratory tests
				• Vital signs
					PD Endpoints:
					IPA:
					• TCG inhibited final-extent ADP-induced platelet aggregation at 2 hours after initial dosing (Day 1) and at steady state (Day 28).
					• On Day 1, peak final-extent IPA was observed 2-4 hours postdose with TCG (~60%-95% IPA), whereas CLP displayed <20% IPA at any time point on Day 1.
					• At steady state, the 3 highest doses of TCG produced peak final-extent mean percentage IPA (~90%-95%) that was greater than that achieved with CLP or TCG 50 mg BID.
					Bleeding times:
					• All doses of TCG increased bleeding times to a greater extent than CLP, but no obvious dose-response was observed.
					PK Endpoints:
					• PK parameters were assessed on Days 1, 14, and 28.
					• Steady state was reached by Day 14.
					• Plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX) increase linearly over time and are dose proportional.
					• At steady state, plasma concentrations of AR-C124910XX were ~35% of ticagrelor.
					PK/PD Relationship:
					• Onset of maximum IPA corresponded with time of maximum plasma concentrations.
					• Increases in dose >100 mg BID resulted in only small additional increases in IPA.
					Safety Endpoints:
					• Most common AE was bleeding.
					  ○ Bleeding occurred at a higher incidence with the 3 higher doses of TCG compared with TCG 50 mg BID and CLP.
					  ○ 1 case of major bleeding in the TCG 400 mg QD group.
					• Other AEs with an incidence of >10%: dyspnea, dizziness, headache, and presence of red blood cells in the urine.
					• Dyspnea appeared to increase with increasing dose of TCG (50 and 100 mg BID: 10%; 200 mg BID: 16%; 400 mg QD: 20%).

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
					○ No episodes were considered serious. ○ No episodes were associated with heart failure or bronchospasm. • Uric acid levels increased by 5-10% in all TCG groups and decreased by ~10% in the CLP group.
ONSET/OFFSET Gurbel et al. *Circulation*. 2009;120:2577-2585.	Phase II multicenter, randomized, double-blind, double-dummy, parallel-group study conducted in the US and UK. **Aim:** to determine the onset and offset of the antiplatelet effect of TCG compared to high LD CLP and placebo in patients with stable CAD treated with ASA.	N=123 **Initial LD (Day 1):** • TCG 180 mg x 1, or • CLP 600 mg x 1, or • Placebo **Maintenance:** TCG 90 mg or placebo in the evening on Day 1, followed by: • TCG 90 mg BID (n=57), or • CLP 75 mg QD (n=54), or • Placebo (n=12) for 6 weeks. All patients received ASA 75-100 mg QD. **OFFSET period:** Following the 6 week treatment phase, patients entered a 10-day drug-offset period during which they were given a final dose of the study drug on the first day of the offset period.	**Inclusion:** • Age ≥18 years • Stable CAD • ASA 75-100 mg/day **Exclusion:** • History of ACS in prior 12 months • Any indication for antithrombotic therapy • CHF • LVEF <35% • FEV_1 or FVC below LLN • Bleeding diathesis • Severe pulmonary disease • Pregnancy • Smoker • Treatment with moderate or strong P450 3A inhibitors, substrates or strong P450 3A inducers • PLT <100,000/mm^3 • Hb <10 g/dL • HbA_{1c} ≥10% • History of drug addiction or alcohol abuse in past 2 years • NSAID • CrCL <30 mL/min	**Primary:** • ONSET: IPA (20 µmol/L ADP, final extent) 2 hours after the first dose • OFFSET: Slope of IPA between 4 and 72 hours after the last dose. **Secondary:** • IPA (final and maximum extent): 5- and 20-µmol/L ADP and 2 µg/mL collagen-induced light-transmittance aggregometry • PRI • ADP-induced GP IIb/IIIa and P-selectin expression • PRU and percent inhibition (VerifyNow $P2Y_{12}$ assay)	**Primary Endpoints:** **Onset:** IPA final extent was greater for TCG than for CLP (88% vs. 38%; p<0.0001). **Offset:** Slope of IPA from 4 to 72 hours after the last dose was greater in the TCG group than in the CLP group (-1.04 vs. -0.48 IPA %/h, p<0.0001). **Secondary Endpoints:** **Onset:** • IPA maximum extent was greater for TCG than for CLP (65% vs. 25%; p<0.0001). • Mean time to maximum IPA was 2.0 hours for TCG and 7.8 hours for CLP. • IPA was greater for TCG than for CLP 0.5 hours after the LD (41% vs. 8%; p<0.0001) and at all time points during the first 24 hours and during the maintenance phase through Week 6 (p<0.0001). • Within 1 hour of the TCG loading dose, IPA was greater than the maximum IPA after the CLP loading dose. • Within 2 hours after loading, a greater proportion of patients achieved >50% IPA (98% vs. 31%, p<0.0001) and >70% IPA (90% vs. 16%, p<0.0001) in the TCG group compared to the CLP group, respectively. **Offset:** • At 24 and 48 hours after the last dose, mean IPA was similar for TCG and CLP (p=NS). At 72 and 120 hours after the last dose, mean IPA was significantly lower (p≤0.05) with TCG. Mean IPA did not differ between groups thereafter. • The time required for IPA to decrease from 30% to 10% in the TCG group was less than half that in the CLP group (53 vs. 116 hours, respectively), and the time to reach 10% was nearly twice as long after CLP discontinuation (109 vs. 196 hours, respectively). • IPA for TCG on Day 3 after the last dose was comparable to CLP at Day 5; IPA on Day 5 for TCG was similar to CLP on Day 7 and

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
					did not differ from placebo (p=NS). **PRU and PRI:** • Greatest change in PRU and PRI from baseline occurred within 2 hours after the TCG LD and 8 hours after the CLP LD. • PRU and PRI were significantly lower with TCG at all time points during the study except ≥48 hours after the final dose. **Expression of PLT Receptors:** • Maximum antiplatelet effect occurred within 2 hours after the TCG LD and 8 hours after the CLP LD (p=NS). • Antiplatelet effect was significantly lower with TCG at all time points during the study except ≥48 hours after the final dose (p<0.05). **Safety:** • Bleeding-related events: TCG=28.1%; CLP=13.0%; placebo=8.3%. • There were no major bleeding events. • Dyspnea likely or possibly due to the study drug occurred in 25%, 4%, and 0% of patients in the TCG, CLP, and placebo groups, respectively (TCG vs. CLP, p<0.01). Three patients in the TCG group withdrew from the study due to dyspnea.
RESPOND Gurbel et al, *Circulation*. 2010b;121:1188-1199. In-House Data, AstraZeneca LP, D5130C00030.	Phase II multicenter, randomized, double-blind, double-dummy, 2-way crossover study in patients with stable CAD treated with aspirin. **Aims:** 1) to investigate the antiplatelet effect of TCG in CLP nonresponders, and 2) to study platelet function during switching from CLP to TCG therapy and vice versa.	N=98 • CLP nonresponders: n=41 • CLP responders: n=57 Definition of CLP nonresponders: ≤10% absolute change in IPA (maximal extent, 20 µM ADP) 6-8 hours after a single dose of 300 mg. Patients randomized to: • TCG: 180 mg x 1, then 90 mg BID, or • CLP: 600 mg x 1, then 75 mg QD for 14±2 days All CLP nonresponders crossed over to the other treatment for an additional 14±2 days. Half of CLP responders	**Inclusion:** • Stable CAD • ASA 75-100 mg QD • Age ≥18 years **Exclusion:** • History of ACS within past 12 months • History of bleeding diathesis or severe pulmonary disease • Pregnancy • Tobacco >1 pack per day • Concomitant therapy within 14 days: strong CYP 450 3A inhibitors or inducers, antithrombotic therapy other than ASA • NSAID use • PLT <100,000 mm^3 • Hb <10 g/dL • Hb A_{1c} ≥10% • CrCL <30 mL/min • History of drug addiction	**Primary:** Proportion of CLP nonresponders who responded to TCG as measured by IPA (20 µM ADP, final extent) >10% 4 hours postdose (In-house data). **Secondary:** Comparison of effect of TCG vs. CLP on various measures of platelet activity such as IPA, PRU, PRI, PLT receptor expression.	34 nonresponders (83%) and 54 responders (95%) completed the study. **Nonresponder Cohort:** • The proportion of CLP nonresponders who achieved >10% final extent IPA on TCG treatment was not significantly different from the proportion achieving this target on CLP treatment. This may have been due to a higher than expected response to CLP after 14 days of treatment in patients initially defined as CLP nonresponders (In-house data). • A greater proportion of CLP nonresponders achieved >10% maximum extent IPA on TCG compared with CLP (p=0.005). • A greater proportion of CLP nonresponders achieved >30% and >50% maximum extent IPA on TCG compared with CLP (p-values both <0.05). • When switched from CLP to TCG, platelet aggregation fell from 59%±9% to 35%±11% (p<0.0001). • When switched from TCG to CLP, platelet aggregation increased from 36%±14% to 56%±9% (p<0.0001). **Responder Cohort:** • Platelet aggregation (20 µM ADP, maximum extent) was significantly lower after TCG compared with CLP 4 hours postdose on Days 1 and 14 of periods 1 and 2 (p<0.0001 in period

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
		continued with the same treatment while the other half switched to the other treatment for 14±2 days. Patients who switched treatments received a LD followed by the maintenance dose. All patients received ASA (75-100 mg daily).	or alcohol abuse in past 2 years		1; p<0.001 in period 2 after crossover). • IPA was significantly higher at all time points with TCG loading and maintenance therapy except period 2, Day 15, 0 hours. After switching from CLP, IPA was maximal within 1 hour after TCG LD. **HPR:** 98%-100% of TCG patients had platelet reactivity below the cut point versus 44%-70% of CLP patients (as measured by platelet aggregation, VerifyNow $P2Y_{12}$ assay, and VASP phosphorylation). **Safety:** • Discontinuation due to AEs: TCG, n=3; CLP, n=2 • Five serious AEs occurred in 4 patients (during or after TCG): MI, hypotension, atrial fibrillation, and bradycardia during therapy; 1 death occurred 30 days after TCG therapy and was not related to treatment. • One major and 3 minor bleeding events during TCG treatment; no bleeding events during CLP treatment. • Dyspnea occurred in 13 TCG and 4 CLP patients. Most episodes of dyspnea occurred early in the study, resolved without intervention, and did not result in discontinuation.
Cardiopulmonary substudy of ONSET/OFFSET Storey et al. *J Am Coll Cardiol.* 2010e;56:185-193.	6-week, prespecified subanalysis (n=123) of the ONSET/OFFSET trial, which evaluated platelet inhibition in patients with stable CAD treated with low-dose ASA. **Aim:** To determine whether treatment with TCG was associated with any substantial change in cardiopulmonary function	N=123 **Treatment:** • **Initial LD (Day 1):** o TCG 180 mg x 1, or o CLP 600 mg x 1, or o PBO • **Maintenance doses:** TCG 90 mg or PBO in the evening on Day 1, followed by: o TCG 90 mg BID (n=57), or o CLP 75 mg QD (n=54), or o PBO (n=12) for 6 weeks. • ASA 75-100 mg QD • After the 6-week treatment phase, patients entered a 10-day drug-offset period; a final dose was given on Day 1 of the offset period.	**Key inclusion criteria:** Patients were required to have received at least 1 dose of study drug. **Key exclusion criteria:** Patients with CHF or significant lung disease were excluded from this subanalysis.	**Endpoints:** Cardiopulmonary assessments, serum biochemistry tests, and PK	• The incidence of dyspnea was 38.6% in the TCG 90 mg BID group (p<0.001 vs. CLP), 9.3% in the CLP group, and 8.3% in the PBO group (TCG vs. CLP, p<0.001; TCG vs.PBO, p<0.05). Dyspnea led to premature D/C in 3 patients in the TCG group and no patients in the CLP group. • Most instances were mild and/or lasted <24 h. In the TCG group, 8 of 22 patients experienced dyspnea within 24 h and 17 of 22 patients experienced dyspnea 1 week after administration. • Dyspnea persisted in a few patients through the study follow-up period, which lasted 10 days after D/C of study medication (n=1, placebo; n=3, TCG; n=3, CLP). • In patients who experienced dyspnea, no significant changes from baseline to 6 weeks were noted in any cardiac measures (BP, heart rate, ECG, LVEF, or BNP) or pulmonary function parameters (such as FEV_1, FVC; FEV_1/FVC, $FEF_{25\%-75\%}$, TLC, RV, tidal volume, or oxygen saturation). • C_{max} and AUC_{0-8} were similar between TCG-treated patients who experienced dyspnea and those who did not.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
Effect of TCG on QT interval Butler et al. *Int J Clin Pharmacol Ther*. 2010;48:643-651.	Single-center, randomized, double-blind, positive-control, 3-period crossover study of healthy volunteers **Aim:** To assess whether a single 900-mg dose of TCG affects the time interval of ventricular depolarization and repolarization (QT interval) in healthy male subjects	N=36 **Treatment:** • Treatment A: single doses of TCG 900 mg with moxifloxacin PBO • Treatment B: single doses of moxifloxacin 400 mg with TCG PBO • Treatment C: single doses of TCG PBO with moxifloxacin PBO 7- to 14-day washout period was used between treatments.	**Inclusion:** • Healthy males aged 18-45 years • BMI=20-28 kg/m^2 **Exclusion:** • Abnormal ECG at screening or enrollment • History of arrhythmia or QT interval prolongation • Heart rate <50 bpm at screening • QT interval >450 milliseconds for QTcF or >480 milliseconds for QTcB • History of heart block	**Primary Endpoint:** Continuous 12-lead resting dECGs were collected over 24 hours after each treatment and corrected for the effect of heart rate on the QT interval by using a study-specific factor (QTcX).	• No relationship between plasma levels of TCG or its metabolite (AR-C124910XX) and QT interval was observed. • A single dose of TCG 900 mg did not prolong the QT interval in healthy subjects.
PK, PD of TCG in patients with mild hepatic impairment Butler et al. *J Clin Pharmacol*. 2011;51:978-987.	Single-center, nonrandomized, open-label, parallel-group, single-dose study **Aim:** To compare the PK of TCG and the active metabolite, AR-C124910XX, in volunteers with mild hepatic impairment versus healthy controls	N=20 (10 with hepatic impairment [Child-Pugh class A] and 10 with normal hepatic function) After an overnight fast, all volunteers received a single 90 mg dose of TCG.	**Key Inclusion Criteria:** • Men or women 18 years or older • Weight ≥50 kg • BMI=18-35 kg/m^2 • Confirmation of stable hepatic impairment **Key Exclusion Criteria:** • Child-Pugh class B or C impairment • Weight <50 kg • Presence/history of condition effecting drug disposition • Any clinically significant ECG findings, laboratory results, or coagulation abnormalities	PK, PD, and safety parameters	**PK/PD Results:** • Absorption of TCG and formation of AR-C124910XX were rapid in both groups. TCG exposure was higher in hepatically impaired volunteers (C_{max}: 12%; $AUC_{0-\infty}$: 23%) vs. controls. AR-C124910XX exposure was also higher in hepatic impairment (C_{max}: 17%; $AUC_{0-\infty}$: 66%). The unbound fraction of TCG was comparable between groups. • Marked interindividual variation in PK parameters was observed for 3 volunteers with hepatic impairment who had much higher exposure to TCG and AR-C12491-XX compared with other subjects. • A nonsignificant trend toward higher mean inhibition of final-extent IPA using ADP 20 µM was observed in the mild hepatic impairment group vs. the control group. • The concentration-effect profiles overlapped for volunteers with mild hepatic impairment and controls for TCG+AR-C124910XX concentrations up to 200 ng/mL. At higher concentrations, the final-extent IPA appeared to be higher in the group with mild hepatic impairment than in volunteers with normal hepatic function. • Overall, increased exposure of TCG and AR-C124910XX was not associated with clinically significant changes in PD. **Safety Results:** TCG was well tolerated; no AEs were reported.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
Effects of gender and age on TCG PK/PD Butler et al. *AAPS J*. 2008;10(S2). Abs T3002. Available at: http://www.aapsj.org/abstracts/AM_2008/AAPS2008-002925.PDF. Accessed July 20, 2011.	Open-label, parallel-group study of the PK/PD of a single 200-mg oral dose of TCG in men and women of various ages (18 to 45 years and ≥65 years) **Aim:** To determine the effects of gender and age on the PK/PD of TCG in healthy subjects	N=40 • 10 men aged 18-45 years • 10 women aged 18-45 years • 10 men aged ≥65 years • 10 women aged ≥65 years **Treatment:** A single 200-mg dose of TCG given orally after an overnight fast	**Inclusion:** • Healthy men and women • Age ranges: 18-45 years, ≥65 years **Exclusion:** Not provided in abstract	PK and PD variables	• $AUC_{0\text{-}inf}$ o TCG $AUC_{0\text{-}inf}$ was 37% higher for women than for men. o TCG $AUC_{0\text{-}inf}$ was 52% higher for eldery subjects than for younger ones. o Similar patterns were observed for the active metabolite AR-C124910XX. • C_{max} o TCG C_{max} was 52% higher for women that for men. o TCG C_{max} was 63% higher for elderly subjects than for younger ones. o Similar patterns were observed for the active metabolite AR-C124910XX. • IPA o >90% mean final-extent inhibition was achieved by 4 hours after dose administration in all groups. o Final-extent inhibition and maximal-extent inhibition were as follows, respectively: ▪ 99.5% and 73.3% in young men ▪ 97.3% and 68.3% in young women ▪ 94.7% and 65.6% in elderly men ▪ 92.9% and 58.7% in elderly women. • Safety and tolerability: Gender- or age-related differences in safety and tolerability of TCG were not apparent.

ACS = acute coronary syndrome; ADP = adenosine-5′-diphosphate; AE = adverse event; ASA = aspirin; AUC = area under the plasma concentration vs. time curve; BMI = body mass index; BNP = N-terminal pro-brain natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; CL/F = total plasma oral clearance; CLP = clopidogrel; C_{max} = maximum plasma concentration; COPD = chronic obstructive pulmonary disease; CrCL = creatinine clearance; CV = cardiovascular; D/C = discontinuation; DLCO = single-breath diffusion lung capacity measured by using carbon monoxide, DM = diabetes mellitus; ECGs = electrocardiograms; $FEF_{25\%\text{-}75\%}$ = mean forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1 = forced expiratory volume in the first second; FRC = forced residual capacity; FVC = forced vital capacity; Hb = hemoglobin; HPR = high platelet reactivity; IPA= inhibition of platelet aggregation; K-M = Kaplan-Meier; LD = loading dose; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; NSTE = non-ST-elevation; PBO = placebo; PCI = percutaneous coronary intervention; PD = pharmacodynamics; PFTs = pulmonary function tests; PK = pharmacokinetics; PLATO = PLATelet inhibition and patient Outcomes; PLT = platelets; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction units; ROW = rest of the world; RRR = relative risk reduction; RV = residual volume; SA = sinoatrial; SCr = serum creatinine; STEMI = ST-elevation myocardial infarction; SVT = supraventricular tachycardia; $t_{½}$ = terminal half-life; TCG = ticagrelor; TLC = total lung capacity; t_{max} = time to C_{max}; UK = United Kingdom; ULN = upper limit of normal; US = United States; VT = ventricular tachycardia.

3.1.4 EVIDENCE FROM SECONDARY SOURCES

Not available

SECTION 4.0 Economic Value and Modeling Report

4.0 ECONOMIC VALUE AND MODELING REPORT

4.1 Abstract

Introduction: A budget impact model (BIM) was developed in order to estimate the impact of ticagrelor utilization for the management of acute coronary syndrome (ACS) in managed care organizations (MCO) and hospitals in the United States (US). This model draws on clinical data obtained from a large population of patients enrolled in the Study of Platelet Inhibition and Patient Outcomes (PLATO), a double-blind, randomized, multi-center, international trial of antiplatelet therapy comparing ticagrelor and clopidogrel. The model used real-world data from administrative datasets for cost of different resource use item/events information.

Methods: Clinical inputs, including the events during the index hospitalization, in the 30 days post index hospitalization, and in the 1-year period after hospitalization (including medical management, CV events/revascularization rates, major bleeding, bed days, and death) were derived from the PLATO trial. The data was obtained on the overall PLATO patient cohort as well as the low-dose aspirin patient cohort, which were identified as patients on aspirin maintenance dose of ≤100mg per day. Cost inputs included in the model include payment (diagnosis-related group [DRG]-based payments and fee-for-service [FFS] payments) amounts and hospital costs incurred (hospital perspective only) for ACS-related medical events such as coronary artery bypass grafts (CABG), percutaneous coronary intervention (PCI), unstable angina (UA) with or without coronary angiography, myocardial infarction (MI) with or without coronary angiography, major bleeding, or stroke. Daily medication costs of ticagrelor and clopidogrel were included and were based on wholesale acquisition costs (WAC).

Results of the analysis are presented as total costs, cost per ACS admission (for hospital setting) and cost per treated plan member per month for the overall PLATO cohort as well as the low-dose aspirin cohort in yearly estimates for up to 3 years after introduction of ticagrelor. The budgetary impact of utilizing ticagrelor is calculated as the total cost (OAP treatment and event management costs) with ticagrelor utilization minus the total cost without ticagrelor (all clopidogrel utilization as described by the current scenario). Other outcomes evaluated include the impact on length of stay, rehospitalizations within 30 days or 12 months (MCO setting), and death due to any cause.

Results:
With a hypothetical MCO cohort of 20,000 patients admitted for ACS each year, ticagrelor uptake of 1%, 3%, and 6% by Years 1, 2, and 3, respectively, and a gradual shift from 75% branded clopidogrel use in year 1 to 100% generic clopidogrel use in the subsequent years was estimated to result in $77.2 million cumulative cost-savings over a 3-year period (or $322 per treated member per month). Over 3 years, the increased ticagrelor use instead of clopidogrel was also estimated to result in approximately 819 fewer bed days (including index hospitalization and subsequent rehospitalizations), 5 fewer ACS-related rehospitalizations in 30-days post index hospitalization discharge, 73 fewer rehospitalizations (related with ACS, stroke and major bleed) occurring within 12 months post-discharge, and 25 fewer deaths (due to any cause). Similar results on the net budget impact and other included outcomes were obtained for the low-dose aspirin cohort using the clinical data for this subgroup in the PLATO trial. In both cases, a reduction in event management costs associated with increased utilization of ticagrelor and cost savings achieved through generic availability of clopidogrel contributed to the overall cost savings.

From a hospital perspective (assuming 2,000 patients hospitalized for ACS annually), Ticagrelor uptake of 4%, 10%, and 14% by Years 1, 2, and 3, respectively, and assuming a gradual shift from 75% branded clopidogrel use in year 1 to 100% generic clopidogrel use in the subsequent years was estimated to result in cumulative cost-savings of $267,992 over a 3-year period. The total length of stay for index ACS hospitalization was also estimated to be reduced by 50 days over the 3-year time horizon. During the 3-year time horizon, increasing the use of ticagrelor within a hospital from 4% to 14% could potentially result in, cumulatively, 2 fewer rehospitalizations, and 2 fewer deaths within the first 30 days post-discharge. Using the efficacy data from the low-dose aspirin cohort similar results were observed.

Model assumptions, limitations and disclaimers: Patients are assumed to be on aspirin along with either clopidogrel or ticagrelor. Patients do not discontinue antiplatelet therapy or switch between ticagrelor and clopidogrel for any reason. Other antiplatelet therapies (e.g., prasugrel) are not evaluated. Other events included within the model are stroke (ischemic) and PLATO-defined major bleeding as observed in the PLATO trial. This model focuses on the most resource-intensive intervention as the primary reimbursement/cost driver – within each admission, the first of each type of additional events or interventions was used for the ascertainment of the final diagnostic-related group (DRG). PLATO-defined minor bleeding while resulting in resource utilization was assumed to be included in the final DRG assessment and, therefore, wasn't

separately included in the model. Patients are followed for up to 30 days/12 months (depending on the perspective) post-index discharge. This model uses a number of exploratory subgroup analyses to populate the model. It should be noted that the results of this model are based on estimates and do not represent confirmed observations. PLATO was not prospectively designed or powered to show that BRILINTA would be more effective than clopidogrel in any of the post-hoc analyses. The results of this model do not guarantee or make any warranties regarding the financial or clinical performance of any oral anti-platelet therapy mentioned within it.

Discussion:

The current budget impact model was developed based on the clinical benefits data from PLATO and real world data for cost estimates. In the MCO scenario with a hypothetical cohort of 20,000 ACS patients, the use of ticagrelor up to 6% over a 3-year period and accounting for availability of generic clopidogrel resulted in an estimated cumulative 3-year cost savings of $77.2 million. The increased use of ticagrelor over this period was estimated to result in 5 fewer 30-day rehospitalizations, 73 fewer 12-month ACS-related rehospitalizations and 25 fewer deaths due to any cause. In the hospital scenario with an estimated 2,000 annual ACS admissions, the use of ticagrelor up to 14% and accounting for generic clopidogrel use over a 3-year period resulted potential cost savings of $267,992. The increased use of ticagrelor over this period was estimated to result in 50 fewer bed days during index hospitalization, 2 fewer 30-day ACS-related re-hospitalization and 2 fewer deaths due to any cause during the 30-day post index discharge follow-up.

4.2 Overview

Ticagrelor is an oral anti-platelet agent which selectively and reversibly inhibits the P2Y12 receptor of adenosine diphosphate (ADP). A large, double-blind, randomized, multi-center, international trial comparing ticagrelor to clopidogrel for the prevention of cardiovascular events in patients hospitalized with ACS was recently completed. Patients receiving ticagrelor were found to experience fewer cardiovascular events as compared to patients receiving clopidogrel (Wallentin 2009). In order to evaluate the medical and pharmacy budget impact of ticagrelor as a new option for management of ACS, a Microsoft® Excel-based BIM was developed. The BIM estimates the financial impact of utilization of ticagrelor as compared to clopidogrel (brand or generic) for the managed care organizations (MCO) as well as hospitals. Patients included in the PLATO trial were all patients hospitalized for acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms in the 24 hours prior to hospitalization. The model calculates the budgetary impact of the use of ticagrelor in terms of the costs of inpatient hospitalization for ACS (the index hospitalization) and any related complications (re-hospitalization, major bleeding, etc.), as well as any related pharmacy costs. Results include total costs, and annual costs for Year 1 following initial uptake, Year 2, and Year 3. Cost results are presented as total costs and cost per treated member per month.

Because not all health plans or ACS patients are the same, the model allows for flexibility in comparisons of different plan sizes, resource utilization, and costs. Results of a potential scenario ("base case") are presented in the following modeling report as a reference for further consideration. Please contact your AstraZeneca representative to request further details.

This model uses a number of exploratory subgroup analyses to populate the model. It should be noted that the results of this model are based on estimates and do not represent confirmed observations. PLATO was not prospectively designed or powered to show that BRILINTA would be more effective than clopidogrel in any of the post-hoc analyses. Subgroup analysis were examined for their influence on outcome. The results of this model do not guarantee or make any warranties regarding the financial or clinical performance of any oral anti-platelet therapy mentioned within it.

4.2.1 Model Features

The table below summarizes the key model features.

Table 4-1. Key Model Features

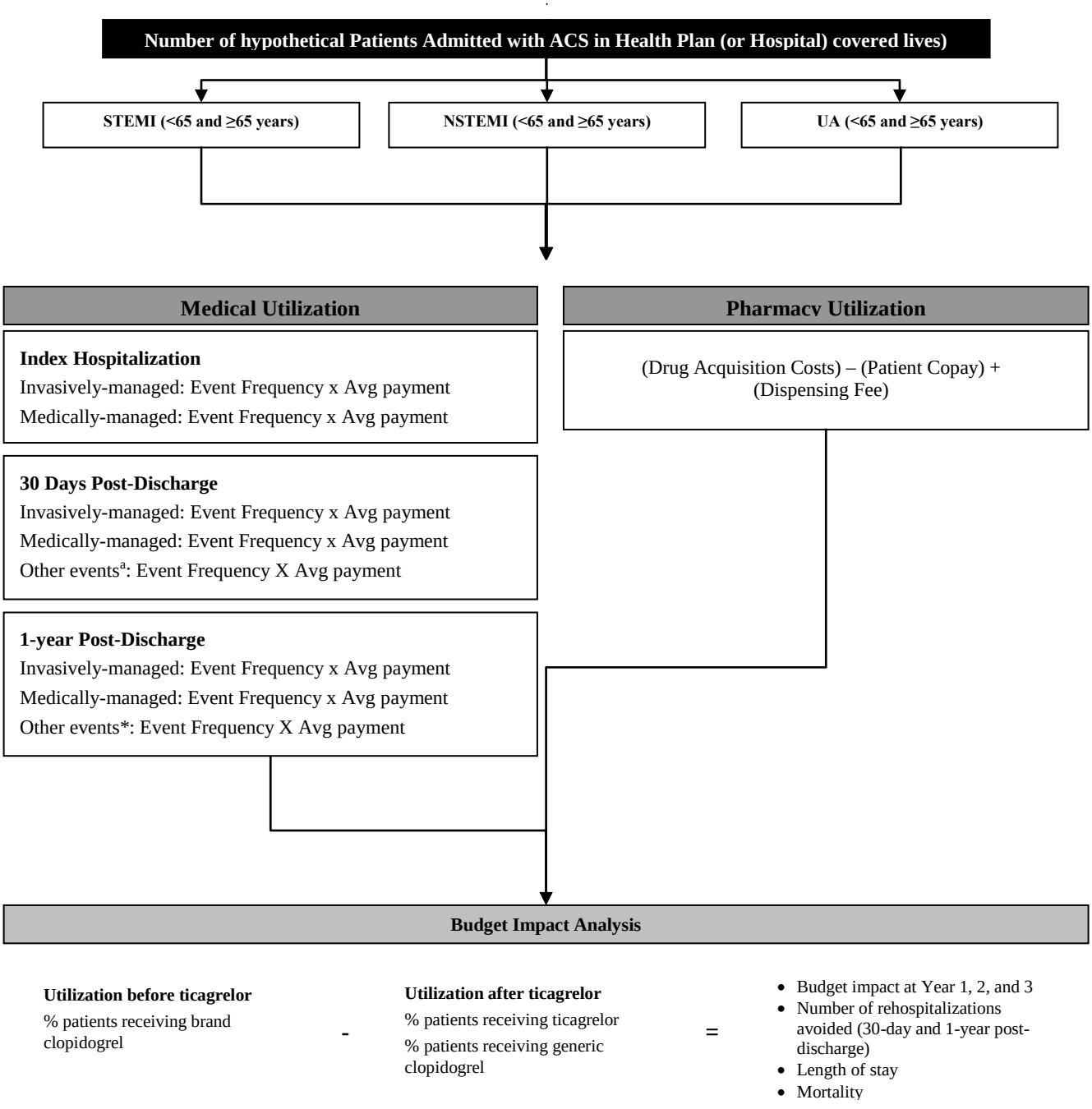
Model Objective	To assess the budget impact of ticagrelor for the management of ACS from a managed care organization (MCO) perspective as well as from a hospital perspective
Patient Population	Patients hospitalized with an ACS event
Comparators	Clopidogrel – brand or generic
Perspective	Hospital or MCO
Time Horizon	1 year post index hospitalization (budget impact is presented for up to 3 years)
Costs	Pre-payment amounts for related events and medication costs
Outcomes	Total plan costs for Years 1, 2 and 3; costs per treated member per month (MCO perspective); total rehospitalizations; length of stay; mortality
Discounting	Due to the short time horizon, no discounting was applied

4.3 Methods

4.3.1 Model Structure

Figure 4-1 provides a schematic depiction of the model structure. Based on a hypothetical plan or hospital population, the number of ACS patients with STEMI, NSTEMI, and unstable angina was determined. Resource utilization for each treatment group (ticagrelor and clopidogrel) was determined during the index hospitalization, and in the 30-day and 1-year period (MCO perspective only) following the index hospitalization. Associated medical and pharmacy costs were determined for each treatment group. Using the projected utilization of ticagrelor, costs were calculated within each treatment group. Pharmacy, medical and total budget impact was estimated within each treatment group and was summed to estimate the budget impact following the adoption of ticagrelor. The budget impact was estimated in total dollars, annual dollars as well as per treated member per month (PTMPM), and per ACS admission.

Figure 4-1. Model Structure



[a]Other events include stroke, major bleeding, and death
Key: ACS = acute coronary syndrome; ; NSTEM = non-ST-segment myocardial infarction; STEMI = ST-segment myocardial infarction; UA = Unstable Angina

4.3.2 Treatment Options

Treatment options in the BIM include ticagrelor and clopidogrel. All baseline drug utilization of agents can be defined by the health plan/hospital; the base case and estimated changes after ticagrelor are based on market research conducted by AstraZeneca. However, all drug utilization assumptions can be further modified to an individual health plan's or hospital's specifications.

4.3.3 Patient Population

The target patient population is patients of either gender, above or below 65 years of age, hospitalized with an ACS event: STEMI, NSTEMI, or unstable angina (UA). The distribution of the patient population by ACS type is determined by patient population enrolled in the PLATO trial. Differential risk of ACS events according to known risk factors, such as age, gender, diabetes or hypertension, was not estimated.

Table 4-2. Description of Patient Population

Patient Characteristics	Input	Source
Number admitted each year with ACS and eligible for antiplatelet treatment	**20,000/2000**	**Defined by health plan/hospital**
<65 years	**55%**	**Wallentin 2009**
≥65 years	**45%**	
ACS type distribution, % (n)		**In House AstraZeneca Data**
STEMI	**38% (7,600/760)**	
NSTEMI	**43% (8,600/860)**	
Angina	**19% (3,800/380)**	
Current use of antiplatelet treatment, % (n)		**Model Assumption**
Branded clopidogrel	**100% (20,000)**	
Generic clopidogrel	**0% (0)**	
Ticagrelor	**0% (0)**	

Key: ACS = acute coronary syndrome; ; NSTEM = non-ST-segment myocardial infarction; STEMI = ST-segment myocardial infarction

4.3.4 Perspective

The BIM has the functionality to evaluate two perspectives: hospital and MCO. In the hospital perspective the budget impact estimation accounted for the events during index hospitalization only. Events during the 30-days post-index hospitalization were used to derive the 30-day quality of care messages. For the MCO perspective, the budget impact estimation included the index hospitalization events as well as any subsequent rehospitalizations during 1-year time period.

4.3.5 Time Horizon

A 1-year time horizon was selected for the MCO perspective while a 30-day post-index hospitalization time horizon was adopted for the hospital perspective within the model. However, the model is structured so as to provide 3 years of cost information based on changing utilization of ticagrelor. Because of the short time frame, no discounting was applied.

4.4 Clinical and Cost Inputs

4.4.1 ACS Events During Index Hospitalization

The index hospitalization begins with the patient presenting with ACS. Patients (STEMI, NSTEMI, or UA) were either invasively managed (i.e., PCI, CABG, or CABG with PCI) or medically-managed. The distribution of procedures performed during the index hospitalization was determined based on results from the PLATO trial. The model assumed that the rate of ACS events and other events of interest vary only by antiplatelet therapy and not by known patient risk factors.

Table 4-3. Events During Index Hospitalization

Event	Input[a]	
	Clopidogrel	Ticagrelor
Invasively-managed patients		
CABG + PCI	**0.4%**	**0.4%**
CABG	**4.2%**	**3.8%**
PCI	**61.3%**	**61.7%**
Medically-managed patients		
UA with coronary angiography	**3.7%**	**4.0%**
UA without coronary angiography	**8.4%**	**7.7%**
MI with coronary angiography	**11.0%**	**11.4%**
MI without coronary angiography	**10.9%**	**10.9%**

[a] Reference: In House AstraZeneca Data

Key: ACS = acute coronary syndrome; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina

4.4.2 Rehospitalizations for Subsequent Events

Patients who survive the index hospitalization are discharged as well as continue participation within the trial were assumed to continue regular use of anti-platelet therapy (ticagrelor or clopidogrel) as part of medical management. The model then evaluates the frequency and costs associated with hospitalizations due to additional ACS events, and related stroke or PLATO defined major bleeding complications for the remainder of the year. It should be noted that the model counts these events/procedures in both the rest of the year as a whole, and within 30 days post-discharge. The latter estimates are tabulated, but are not costed separately, so as to avoid double-counting. Patients who survive this year then exit the model. The model assumes that patients do not discontinue or switch anti-platelet therapy for any reason.

The distribution of procedures performed during 1-year period following the index hospitalization was determined based on results from the PLATO trial.

Table 4-4. Frequency of Post-Discharge Events (% of Patients)

Event	Events within 30 Days Post-Discharge[a]		Events within 12 Months Pots-Discharge	
	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor
Invasively-managed patients				
CABG + PCI	**0.0%**	**0.1%**	**0.0%**	**0.1%**
CABG	**1.9%**	**1.7%**	**5.3%**	**5.0%**
PCI	**3.8%**	**3.7%**	**13.5%**	**12.7%**
Medically-managed patients				
Angina with coronary angiography	**0.2%**	**0.2%**	**0.6%**	**0.6%**
Angina without coronary angiography	**0.7%**	**0.7%**	**2.4%**	**2.3%**
MI with coronary angiography	**0.1%**	**0.2%**	**0.5%**	**0.6%**

MI without coronary angiography	**0.4%**	**0.2%**	**2.0%**	**1.5%**
Other Events				
Stroke	**0.1%**	**0.1%**	**0.6%**	**0.8%**
Major bleeding	**0.3%**	**0.1%**	**0.8%**	**0.6%**
Death	**0.8%**	**0.5%**	**4.2%**	**2.9%**

[a] Reference: In House AstraZeneca Data

Key: ACS = acute coronary syndrome; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention

4.4.3 Costs and Pre-payments of Events

For the MCO perspective, payments made for the treatment of ACS and other events of interest among plan members were estimated for a pre-payment plan as well as a fee-for-service (FFS) plan. The average payment estimates for each ACS event were obtained from Thomson Reuters MarketScan Research Databases. While the model can accommodate a blended view of FFS and prepayment plan, in the base case scenario no patients were assumed to be in a fee-for-service payment scheme. The model also includes prepayment estimates for Commercial population (<65 years) and Medicare population (≥65 years) for each ACS event and other events of interest.

Table 4-5. MCO Perspective: Pre-Payment Amounts

Event	DRG-based payment (<65 years)[a]	Medicare payment (≥65 years)[b]	FFS
Invasively-managed ACS events			
CABG + PCI	$74,436	$45,835	$62,677
CABG	$42,841	$36,176	$45,584
PCI	$17,210	$17,690	$17,731
Medically-managed ACS events			
Angina with coronary angiography	$8,917	$7,730	$8,999
Angina without coronary angiography	$4,787	$3,776	$3,994
MI with coronary angiography	$12,320	$9,929	$11,095
MI without coronary angiography	$12,320	$9,929	$11,095
Other events			
Stroke	$11,984	$8,506	$11,076
Major bleeding	$7,217	$6,900	$6,582

[a] Reference: MarketScan. Capitated Sources (commercial population). 2008
[b] Reference: MarketScan. Capitated Source (Medicare population). 2008.

Key: CABG = coronary artery bypass graft; DRG = Diagnosis Related Groups; FFS = Fee For Service; MI = myocardial infarction; PCI = percutaneous coronary intervention

From the hospital perspective, in addition to the average pre-payment amount that the hospital receives from commercial payers or Medicare, the BIM accounts for the actual cost of managing an event to the hospital. Estimates for the costs incurred by the hospital were obtained by analyzing the charges for ACS events from the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) data. These costs are shown in the table below.

Table 4-6. Hospital Perspective: Costs and Pre-Payment Amounts

Event	Cost to the hospital[a]
Invasively-managed patients	
CABG + PCI	$47,458
CABG	$35,363
PCI	$14,932
Medically-managed patients	
Angina with coronary angiography	$7,963
Angina without coronary angiography	$3,755
MI with coronary angiography	$8,821
MI without coronary angiography	$8,821
Other events	
Stroke	$8,100
Major bleeding	$5,995

[a] Reference: Nationwide inpatient sample (NIS). 2008.

Key: CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention

4.4.4 Cost of Medication

The average daily cost of medication (clopidogrel and ticagrelor) is based on the wholesale acquisition cost (WAC), and any relevant dispensing fees, and patient copayments. The net daily cost is calculated as the WAC plus the pharmacy dispensing fee, and minus the patient copayment. For the base case scenario, the patient copayment was not included in the analysis (conservative assumption for ticagrelor) The acquisition cost of branded clopidogrel and ticagrelor were obtained from Analy$ource Online, selected from National Drug Data File (NDDF) data, included with permission and copyrighted by First DataBank, Inc., 2011; the acquisition cost of generic clopidogrel was assumed to be $0.50 for 75mg tablet and $2.00 for 300mg tablet (hospital perspective only).

Table 4-7. Daily Medication Costs

Medication Costs	Plavix® 75 mg	Clopidogrel (generic)	Ticagrelor	Source
WAC (daily)	**$6.45**	**$0.50**	**$7.68**	**Analy$ource Online, First DataBank 2011**
Dispensing fee	**$0.00**	**$0.00**	**$0.00**	**User input**
Copayment	**$0.00**	**$0.00**	**$0.00**	**User input**
Net daily cost	**$6.45**	**$0.50**	**$7.68**	**Calculated**

Key: WAC = weighted average unit cost

For the hospital perspective, the cost of medications included the cost of a loading dose (300mg) for clopidogrel and accounted for the average length of stay (LOS) for which antiplatelet treatment would be required. The average LOS was calculated as the LOS incurred for each type of ACS event, weighted by the proportion of ACS events of each type, for patients treated with clopidogrel (8.0 days for clopidogrel and 7.9 days for ticagrelor). Based on a 300 mg loading dose of clopidogrel, the total cost per initial admission for branded clopidogrel was $77.38; the cost per admission for ticagrelor was $68.51.

4.4.5 Length of Stay

The model also calculates the total number of bed days associated with the initial ACS hospitalization and subsequent rehospitalizations for patients receiving either clopidogrel or ticagrelor. The length of stay for individual events was calculated based on data from the PLATO trial. In PLATO, the average length of stay incurred with each type of ACS event (weighted by the proportion of ACS events for each type) for patients treated with clopidogrel was 8.0 days. The average length of stay for a rehospitalization within 30 days was 9.3 days (hospital only) and 8.8 days for rehospitalization during rest of the year (MCO only) in the PLATO trial. The model then applied the proportional change in the length of stay as observed in PLATO for patients receiving ticagrelor compared to those receiving clopidogrel: -1.0% in the initial hospitalization (7.9 days for ticagrelor), -7.0% in rehospitalizations within 30 days (8.6 days for ticagrelor) and -2.0% in rehospitalizations during rest of the year (8.6 days for ticagrelor).

4.5 Model Assumptions

Patients are assumed to be on aspirin along with either clopidogrel or ticagrelor. Patients do not discontinue antiplatelet therapy or switch between ticagrelor and clopidogrel for any reason. Other antiplatelet therapies (e.g., prasugrel) are not evaluated. Other events included within the model are stroke (ischemic) and PLATO-defined major bleeding as observed in the PLATO trial. This model focuses on the most resource-intensive intervention as the primary reimbursement/cost driver – within each admission, the first of each type of additional events or interventions was used for the ascertainment of the final diagnostic-related group (DRG). PLATO-defined minor bleeding while resulting in resource utilization was assumed to be included in the final DRG assessment and, therefore, wasn't separately included in the model. Patients are followed for up to 30 days/12 months (depending on the perspective) post-index discharge.

4.6 Results

The following section describes the budget impact model results for a managed care organization (MCO) and hospital perspective. The net impact on budget for each year is presented as a difference between the current year (Aug'2010-July'2011), defined as 100% branded clopidogrel, and a particular year depicting year 1, 2 or 3. The year 1 would include the timeframe of August 2011 (market availability of ticagrelor) to July 2012. The results are presented based on PLATO trial clinical findings in the patient cohort with 12 months follow-up eligibility irrespective of aspirin dose. In addition, the budget impact was also estimated based on PLATO trial data for patient cohort with maintenance aspirin dose of ≤100 mg/day.

Table 4-8. Base Case Market Distribution of Ticagrelor and Clopidogrel Over 3 Years: MCO and Hospital Perspective

Perspective	Brand Clopidogrel Utilization	Generic Clopidogrel Utilization	Ticagrelor Utilization
MCO			
Current	100%	0%	0%
Year 1	75%	25%	1%
Year 2	0%	100%	3%
Year 3	0%	100%	6%
Hospital			
Current	100%	0%	0%
Year 1	75%	25%	4%
Year 2	0%	100%	10%
Year 3	0%	100%	14%

*The percentage across rows may not add up to 100

4.6.1 MCO Perspective

The following scenario represents a base case for a managed care organization with a hypothetical cohort of 20,000 ACS patients. The base case analysis projects the budget impact of a gradual uptake of ticagrelor to 6% use over a 3 year period, instead of clopidogrel (and after accounting for anticipated generic availability of clopidogrel). The distribution of patients on different OAP treatment was estimated based on utilization levels of ticagrelor and clopidogrel (branded and generic) in each year, as shown in Table 4-9.

Rehospitalizations, Mortality and Bed Days

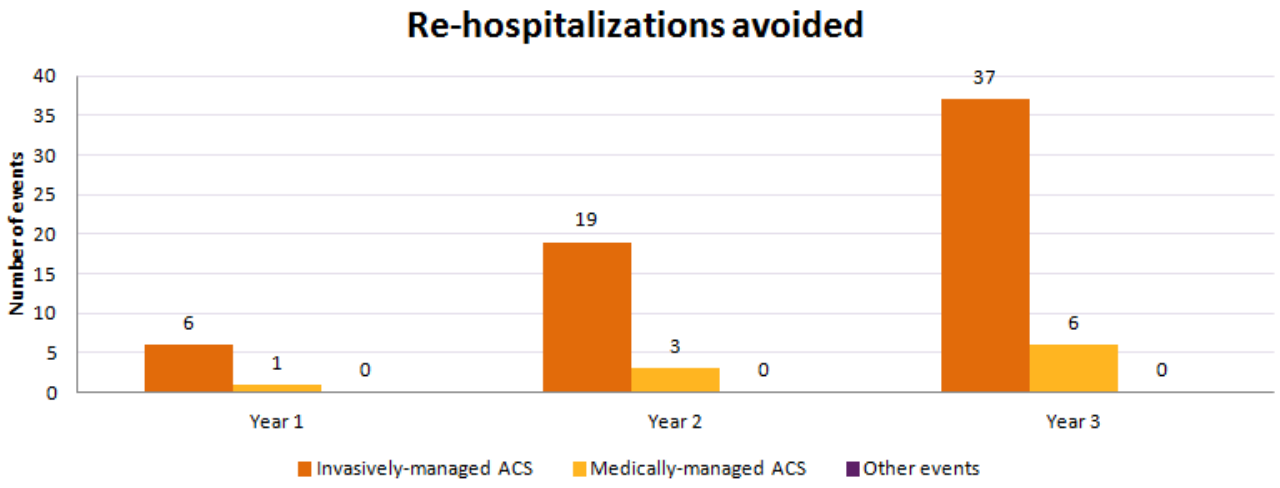
Differences in the number of rehospitalizations, deaths, and bed days are provided in the table below for the current scenario (without ticagrelor) and Years 1-3 (with ticagrelor) in the overall PLATO cohort.

Table 4-9. Impact of Ticagrelor Utilization on Clinical Events

	Current Scenario	Year 1	Year 2	Year 3
Rehospitalizations				
Rehospitalizations within 30-days post-index	1,479	1,478	1,477	1,475
Rehospitalizations within 12-months post-index	5246	5239	5224	5203
Mortality				
Deaths during the first 30 days	169	168	167	165
Deaths during the 12 months post-discharge	831	828	823	816
Bed Days				
During the first 30 days	13,587	13,576	13,555	13,523
During the 12 months post-discharge	46,825	46,761	46,634	46,443

As shown in the figure below, use of ticagrelor may avoid rehospitalizations in both medically- and invasively-managed ACS.

Figure 4-2. Re-hospitalizations Avoided (MCO Perspective)



Key: ACS = acute coronary syndrome

Similar results were observed using the efficacy data from the PLATO trial low-dose aspirin cohort (maintenance dose ≤100mg). At year 3, a 6% ticagrelor use resulted in 6 fewer rehospitalizations, 4 fewer deaths, and 183 fewer bed days within 30-days post-index discharge. These estimates were 43 fewer rehospitalizations, 15 fewer deaths, and 446 fewer bed days during rest of the year post-index hospitalization.

Budget Impact

With the anticipated uptake of ticagrelor (as in Table 4-8), a managed care organization may expect cost-savings for their pharmacy and medical budget (Key: OAP = Oral Antiplatelet

Figure 4-3). Annual and cumulative (net budget impact added over years) budget impact is presented in Figure 4-3. As shown in

Table 4-10, the cost-savings is driven by reduced treatment costs (from increased use of generic clopidogrel) and a reduction in ACS-related events.

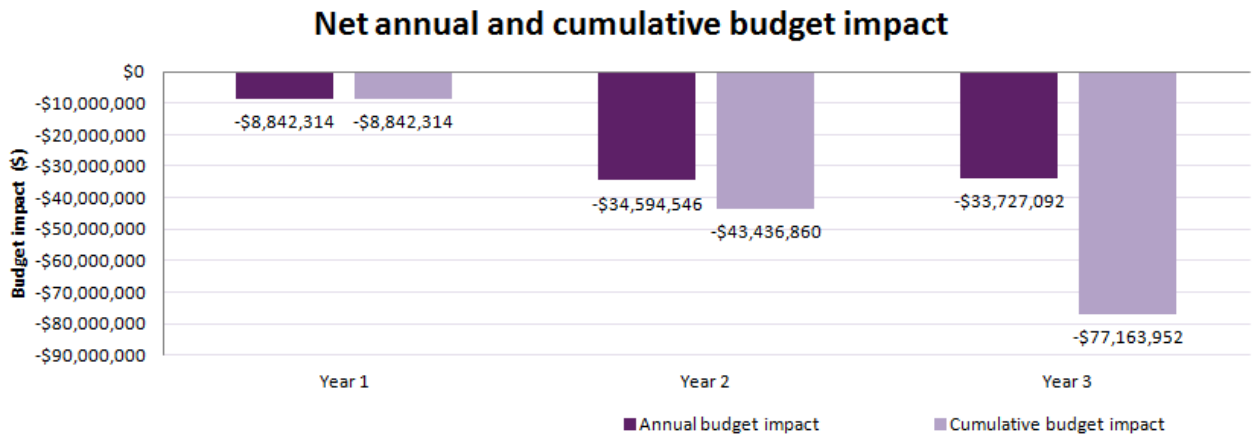
Table 4-10. Impact of Ticagrelor Utilization on Overall (Pharmacy + Medical) Budget: MCO Perspective

	Current Scenario	Year 1	Year 2	Year 3
Total Costs	$460,217,937	$451,375,623	$425,623,391	$426,490,844
Treatment (OAP Therapy) costs	$38,442,000	$29,738,463	$4,263,784	$5,547,568
Event costs	$421,775,937	$421,637,160	$421,359,607	$420,943,276

Key: OAP = Oral Antiplatelet

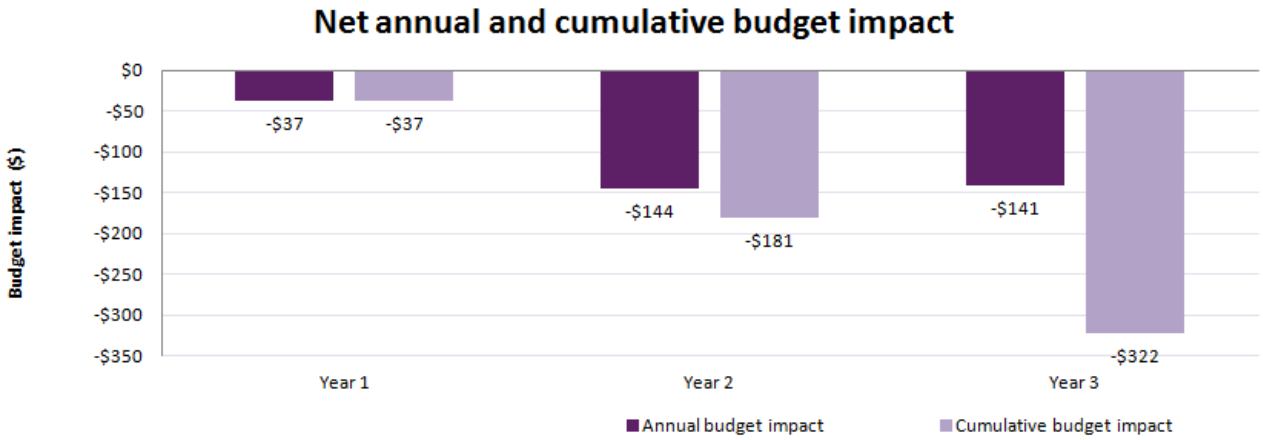
Figure 4-3. Net* Annual and Cumulative Budget Impact, Overall (a) and Per Treated Member Per Month (b)

a)



*Net budget impact calculated as the sum of antiplatelet treatment and ACS event management in the scenario with ticagrelor minus the current scenario, accounting for pre-payments received by the hospital.

b)



*Net budget impact calculated as the sum of antiplatelet treatment and ACS event management in the scenario with ticagrelor minus the current scenario, accounting for pre-payments received by the hospital.

In the first year (1% ticagrelor uptake; 25% of clopidogrel use is generic) a cost-saving of $8.8 million, or $37 per treated member per month was estimated. Over a 3-year period, with ticagrelor use level reaching 6% and clopidogrel being 100% generic, $77.2 million in cost-savings (or $322 per treated member per month) may be realized by an MCO. Over the entire 3-year period, however, oral antiplatelet costs still remained a fraction of the total costs of ACS event management (4%) compared to the current scenario (8%), which included only branded clopidogrel.

Similar results were observed using the efficacy data from the PLATO trial low-dose aspirin cohort (maintenance dose ≤100mg). In the first year (1% ticagrelor uptake; 25% of clopidogrel use is generic) a cost-savings of $8.8 million, or $37 per treated member per month were estimated. Over a 3-year period, with ticagrelor use level reaching 6% and clopidogrel being 100% generic, $76.5 million in cost-savings (or $319 per treated member per month) may be realized by an MCO.

4.6.2 Hospital Perspective

The following scenario represents a base case for a hospital with a hypothetical cohort of 2,000 ACS admissions. The base case analysis projects the budget impact of a gradual uptake of ticagrelor to 14% use over a 3 year period, instead of clopidogrel (and after accounting for anticipated generic availability of clopidogrel). The distribution of patients on either OAP treatment was estimated based on utilization levels of ticagrelor and clopidogrel (branded and generic) in each year, as shown in Table 4-9. The model results are presented for index hospitalization and for up to 30-days post index-hospitalization discharge.

Rehospitalizations, Mortality and Bed Days

From a hospital's perspective, the use of ticagrelor could cumulatively over 3-years avoid 2 rehospitalizations within 30-days post-index discharge. As shown in Table 4-11, the total length of stay for index ACS hospitalizations could be reduced as ticagrelor use increases. In the first year after availability, 7 bed days could be avoided and by Year 3, a total of 25 bed days could be avoided for the index hospitalization. Differences in the number of rehospitalizations, deaths, and bed days are provided in the table below for the current scenario (without ticagrelor) and Years 1-3 (with ticagrelor).

Table 4-11. Impact of Ticagrelor Utilization on Clinical Events within 30 days Post-discharge

	Current Scenario	Year 1	Year 2	Year 3
Rehospitalizations	148	148	147	147
Number of deaths	17	17	16	16
Index Hospitalization Bed Days	15,987	15,980	15,969	15,962

Budget Impact

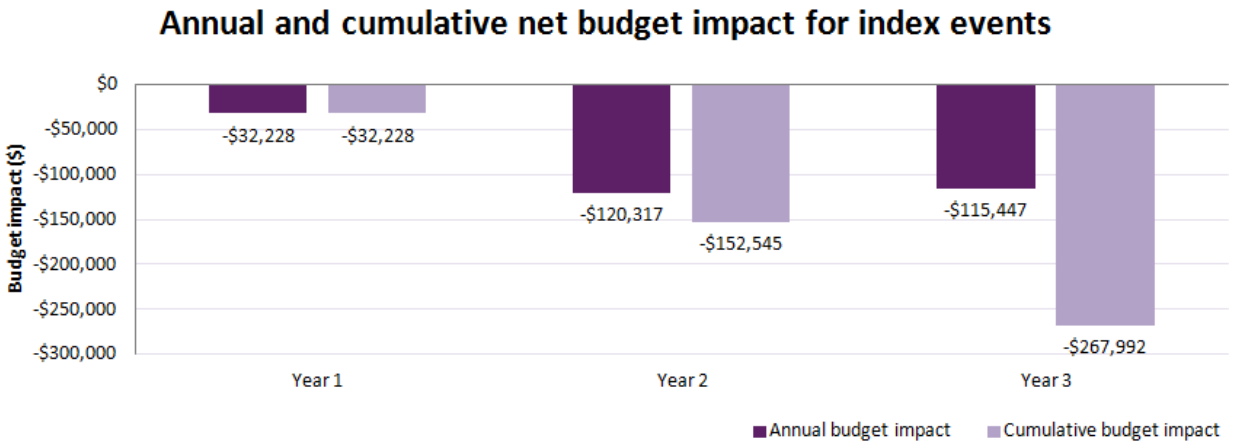
With the anticipated uptake of ticagrelor, a hospital may expect cost-savings for their pharmacy and medical budget (Figure 4-4). As shown in Table 4-12, the cost-savings is driven not only by reduced treatment costs (from increased use of generic clopidogrel), but also by a reduction in event management costs. Over the entire 3-year period, oral antiplatelet costs still remain a fraction of the total costs of ACS event management to the hospital (0.3% of total ACS event management costs).

Table 4-12. Impact of Ticagrelor Utilization on Overall (Pharmacy + Medical) Budget: Hospital Perspective

	Current Scenario	Year 1	Year 2	Year 3
Total Costs	$27,344,647	$27,309,586	$27,217,246	$27,219,282
Treatment costs	$143,629	$110,985	$22,272	$26,726
Event costs	$27,201,018	$27,198,601	$27,194,974	$27,192,556

Pre-payments Received	$31,991,739	$31,988,905	$31,984,655	$31,981,821

Figure 4-4. Net* Annual and Cumulative Budget Impact: Hospital Perspective



*Net budget impact calculated as the sum of antiplatelet treatment and ACS event management in the scenario with ticagrelor minus the current scenario, accounting for pre-payments received by the hospital.

In the first year, 4% ticagrelor uptake and 25% generic clopidogrel may result in a cost savings of $32,228. Over a 3-year period, a hospital may recognize $267,992 in cost-savings with the uptake of ticagrelor and generic availability of clopidogrel.

Similar results were observed using the efficacy data from the PLATO trial low-dose aspirin cohort (maintenance dose ≤100mg). In the first year (1% ticagrelor uptake; 25% of clopidogrel use is generic) a budget impact of $32,589 was estimated. Over a 3-year period, with ticagrelor use reaching 14% and clopidogrel use being entirely generic, $271,285 in cost-savings may be realized by the hospital.

4.7 Discussion and Limitations

The BIM has limitations common to traditional economic modeling involving a variety of assumptions regarding the disease, treatment patterns, and costs. It should be noted that model inputs depend largely upon data collected through the PLATO trial. Though this was a multi-center, international trial, including 18,624 patients from 862 centers in 42 countries, the results obtained through this clinical trial may be different than the effectiveness of ticagrelor in a real-world clinical practice. However, the broad range of patients included in the trial may make these results more generalizable to the ACS patient population. The model considers only the most resource-intensive treatment-related adverse events (e.g., major bleed). This model uses a number of exploratory subgroup analyses to populate the model. It should be noted that the results of this model are based on estimates and do not represent confirmed observations. PLATO was not prospectively designed or powered to show that BRILINTA would be more effective than clopidogrel in any of the post-hoc analyses. The results of this model do not guarantee or make any warranties regarding the financial or clinical performance of any oral anti-platelet therapy mentioned within it.

The current budget impact model was developed based on the clinical benefits data from PLATO and real world data for cost estimates. In the MCO scenario with a hypothetical cohort of 20,000 ACS patients, the use of ticagrelor up to 6% over a 3-year period and accounting for availability of generic clopidogrel resulted in an estimated cumulative 3-year cost savings of $77.2 million. The increased use of ticagrelor over this period was estimated to result in 5 fewer 30-day rehospitalizations, 73 fewer 12-month ACS-related rehospitalizations and 25 fewer deaths due to any cause. In the hospital scenario with an estimated 2,000 annual ACS admissions, the use of ticagrelor up to 14% and accounting for generic clopidogrel use over a 3-year period resulted potential cost savings of $273,992. The increased use of ticagrelor over this period was estimated to result in 50 fewer bed days during index hospitalization, 2 fewer 30-day ACS-related re-hospitalization and 2 fewer deaths due to any cause during the 30-day post index discharge follow-up.

References

Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *NEJM*. 2009;361(11):1045-1057.

Analy$ource Online, selected from National Drug Data File (NDDF) data, included with permission and copyrighted by First DataBank, Inc., 2011

Brilinta (ticagrelor) Prescribing Information. AstraZeneca. Wilmington, DE: July 2011.

SECTION 5.0 Other Supporting Evidence

5.1 SUMMARY OF OTHER RELEVANT EVIDENCE

5.1.1 PUBLISHED AND UNPUBLISHED STUDIES SUPPORTING LABELED AND OFF-LABEL INDICATIONS

5.1.1.1 Published and Unpublished Clinical Studies for Labeled and Off-label Indications

Phase III Studies

Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes. The PLATO (PLATelet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol.* 2010a;56:1456-1462.

Storey RF, Angiolillo DJ, Patil SB, et al. Online appendix. *J Am Coll Cardiol.* 2010b;56:1456-1462. Available at: http://content.onlinejacc.org/cgi/content/full/j.jacc.2010.03.100/DC1. Accessed July 20, 2011.

Objective: To assess the onset and extent of inhibition of platelet function in PLATO study patients

LD Analysis

Methods:

- Effects of LDs on platelet function were evaluated in 24 clopidogrel-naïve patients (ie, patients who had not received clopidogrel in the previous 14 days) enrolled in the PLATO trial at a single center.
- Patients received clopidogrel 300 mg LD (n=7), clopidogrel 600 mg LD (n=5), or ticagrelor 180 mg LD (n=12).
- Inhibition of platelet function was measured by light transmittance aggregometry (LTA; ADP 5 and 20 µM, maximal and final extent), VerifyNow® P2Y12 assays, and vasodilator-stimulated phosphoprotein (VASP) phosphorylation assays.
- LTA was performed prior to drug administration and 1, 2, 4, 8, and 12 hours after drug administration. VerifyNow $P2Y_{12}$ and VASP phosphorylation assays were performed prior to and 4 hours after drug administration.
- Concomitant medication use at the time of LD administration is shown in the following table.

TABLE 5-1: Medications Used Concomitantly With Study Drugs at the Time of LD Administration. Adapted from *J Am Coll Cardiol.* 2010;56:1456-1462.

Drug Type	Ticagrelor LD Group n=12 n (%)	Clopidogrel LD Group n=12[a] n (%)	p-value
ASA[b]	12 (100)	11 (92)	0.47
ACE-Is	2 (17)	5 (42)	0.37
Beta-blockers	2 (17)	3 (25)	1.00
Calcium channel blockers	0 (0)	2 (17)	0.47
Nitrates	5 (42)	3 (25)	0.66
Statins	3 (25)	2 (17)	0.59
Proton pump inhibitors	2 (17)	3 (25)	1.00

ACE-Is = angiotensin-converting enzyme inhibitors; ASA = aspirin; LD = loading dose. [a] Patients received clopidogrel 300 mg LD (n=7) or clopidogrel 600 mg LD (n=5). [b] The mean dose of ASA was 306 mg for the ticagrelor group and 293 mg for the clopidogrel group.

Results:

- More rapid and greater inhibition of platelet function during the first hours of treatment was observed with ticagrelor LD than with either clopidogrel LD.
- At 1 hour after dose administration, all but 1 patient treated with a ticagrelor LD demonstrated greater inhibition of platelet function (ADP 20 µM, maximum and final extent) that was sustained until 12 hours after dose administration.

- Onset of effect was delayed 4 to 8 hours after administration in 1 patient with an inferior STEMI who received a ticagrelor LD.

- Results of the VerifyNow P2Y12 assays showed significantly greater inhibition with the ticagrelor LD than with the clopidogrel LD at 4 hours after dose administration ($p<0.01$). In contrast, the results of the VASP phosphorylation assays showed a nonsignificant trend toward greater inhibition by ticagrelor at 4 hours after dose administration.

- When measures of inhibition of platelet function were evaluated in relation to the thresholds of ischemic risk, there were few poor responders in the ticagrelor group after LD administration; poor response was fairly common in patients given clopidogrel LD (see the following table).

TABLE 5-2: Percentages of Patients With Platelet Function Responses That Were Obtained After LD Administration and Exceeded Risk Thresholds for Ischemic Events. Adapted from *J Am Coll Cardiol.* 2010a;56:1456-1462.

Risk Threshold for Ischemic Event	Time of Sampling	No. of Pts/Total (%) at Risk of Ischemic Event		p-value
		Ticagrelor	Clopidogrel	
Maximal response (LTA) to 20 μM ADP >50%	1 h after LD	1/11 (9)	5/8 (63)	0.04
	2 h after LD	1/8 (13)	6/9 (67)	0.05
	4 h after LD	1/10 (10)	5/8 (63)	0.04
	8 h after LD	1/10 (10)	6/9 (67)	0.02
	12 after LD	0/10 (0)	4/8 (50)	0.02
Final response (LTA) to 5 μM ADP >14%	1 h after LD	2/11 (18)	5/8 (63)	0.07
	2 h after LD	0/8 (0)	4/9 (44)	0.08
	4 h after LD	1/10 (10)	2/8 (25)	0.56
	8 h after LD	1/10 (10)	4/9 (44)	0.14
	12 h after LD	1/9 (11)	4/9 (44)	0.29
VerifyNow P2Y12 >235 PRUs	4 h after LD	1/8 (13)	6/9 (67)	0.05
VASP PRI >50%	4 h after LD	3/11 (27)	4/7 (57)	0.33

ADP = adenosine diphosphate; LD = loading dose; LTA = light transmittance aggregometry; PRI = platelet reactivity index; PRU = platelet reaction units; pts = patients; VASP = vasodilator-stimulated phosphoprotein.

- The onset of IPA, as determined from the LTA data, was more rapid for ticagrelor LD than for clopidogrel LD.

- IPA at 1, 2, and 4 hours following LD administration was significantly greater for the ticagrelor group than for the clopidogrel group. One hour after LD administration, IPA (maximum response to 20 μM ADP) was 54%±23% for the ticagrelor group and 25%±17% for the clopidogrel group ($p<0.01$).

Safety Results: No additional safety results were presented.

Maintenance Dose Analysis

Methods:

- 69 patients enrolled in the PLATO study at 2 centers were included in this analysis of maintenance dosing.

- Patients received ≥28 days of either clopidogrel 75 mg once daily (n=32) or ticagrelor 90 mg twice daily (n=37).

- Patients who participated in the LD analysis also participated in the analysis of maintenance doses.

- Inhibition of platelet function was measured predose (trough) and 2 and 4 hours postdose (peak) by using LTA, VerifyNow $P2Y_{12}$, and VASP phosphorylation assays.

- The percentages of patients in the treatment groups whose LTA responses were associated with an increase in risk of an ischemic event were determined by comparison with the following, previously established thresholds: a maximum LTA response to 20 μM ADP >50% and a final LTA response to 5 μM ADP >14%.

- Concomitant medication use at the time of blood sampling after more than 28 days of maintenance therapy is shown in the following table.

TABLE 5-3: Medications Used Concomitantly With Study Drugs at the Time of Blood Sampling After 28 Days of Maintenance Therapy. Adapted from *J Am Coll Cardiol.* 2010a;56:1456-1462.

Drug Type	Ticagrelor Group n=37 n (%)	Clopidogrel Group n=32 n (%)	p-value
ASA[a]	35 (95)	31 (97)	1.00
ACE inhibitors	32 (87)	26 (81)	0.74
Beta-blockers	28 (76)	29 (91)	0.12
Calcium channel blockers	4 (11)	6 (19)	0.49
Nitrates	27 (73)	22 (69)	0.79
Statins	36 (97)	31 (97)	1.00
Proton pump inhibitors	12 (32)	13 (41)	0.46

ACE = angiotensin-converting enzyme; ASA=aspirin; pts = patients. [a] The mean ASA dose was 98 mg for the ticagrelor group and 108 mg for the clopidogrel group.

Results:

- Results of the LTA, VerifyNow P2Y12, and VASP phosphorylation assays of samples obtained immediately before maintenance dose administration (trough concentration) and 2 to 4 hours after maintenance dose administration (peak concentration) indicated that maintenance therapy with ticagrelor 90 mg twice daily achieved greater and more consistent inhibition of platelet function than did clopidogrel 75 mg once daily.

- Similar patterns of platelet function inhibition were seen in comparisons of ticagrelor and clopidogrel groups in the United Kingdom with those in the US.

- When measures of inhibition of platelet function after maintenance dose administration were evaluated in relation to thresholds of ischemic risk, few poor responders in the ticagrelor group were found; poor response was fairly common in patients given clopidogrel (see the following table).

TABLE 5-4: Percentages of Patients With Platelet Function Responses That Were Obtained After Maintenance Dose Administration and Exceeded Risk Thresholds for Ischemic Events. Adapted from *J Am Coll Cardiol.* 2010a;56:1456-1462.

Risk Threshold for Ischemic Event	Time of Sampling	No. of Pts/Total (%) at Risk of Ischemic Event		p-value
		Ticagrelor	Clopidogrel	
Maximal response (LTA) to 20 μM ADP >50%	Before MD	3/35 (9)	18/31 (58)	<0.0001
	2-4 h after MD	1/37 (3)	13/31 (42)	0.0001
Final response (LTA) to 5 μM ADP >14%	Before MD	4/34 (12)	15/31 (48)	0.02
	2-4 h after MD	0/36 (0)	7/31 (23)	0.01
VerifyNow P2Y12 >235 PRUs	Before MD	1/34 (3)	13/29 (45)	0.0001
	2-4 h after MD	0/36 (0)	12/31 (39)	<0.0001
VASP PRI >50%	Before MD	3/34 (9)	17/25 (68)	<0.0001
	2-4 h after MD	1/33 (3)	13/25 (52)	<0.0001

ADP = adenosine diphosphate; LD = loading dose; LTA = light transmittance aggregometry; MD = maintenance dose; pts = patients; PRI = platelet reactivity index; PRU = platelet reaction units; VASP = vasodilator-stimulated phosphoprotein.

- Comparison of the results of the VerifyNow P2Y12 assays showed similarity in inhibition of platelet function between high-dose and low-dose ASA users within each treatment group after more than 28 days of maintenance therapy (see the following table).

TABLE 5-5: Effects of Low- and High-dose ASA on Inhibition of Platelet Function in Patients Receiving Either Ticagrelor or Clopidogrel Maintenance Therapy. Adapted from Online appendix. *J Am Coll Cardiol.* 2010b;56:1456-1462. Available at: http://content.onlinejacc.org/cgi/content/full/j.jacc.2010.03.100/DC1.

Treatment Group	VerifyNow P2Y12 Results at 2-4 h After Dose Administration (PRU)		p-value
	High-dose ASA[a]	Low-dose ASA[a]	
Ticagrelor[b]	28±28	32±33	NS
Clopidogrel[c]	221±97	192±96	NS

ASA = aspirin; NS = not significant; PRU = platelet reaction units. [a] High doses of ASA were 300-325 mg daily, and low doses were 75-81 mg daily. [b] 3 patients received high-dose ASA; 31 received low-dose ASA. [c] 4 patients received high-dose ASA, and 27 received low-dose ASA.

- Platelet function responses in LTA and VerifyNow P2Y12 assays were greater for patients who received clopidogrel and a PPI than for those who received clopidogrel but no PPI. Platelet function responses did not differ between patients given ticagrelor and a PPI and those given ticagrelor but no PPI (see the following table).

TABLE 5-6: Platelet Function Responses During Maintenance Therapy in Patients Who Received PPIs and in Patients Who Did Not. Adapted from *J Am Coll Cardiol.* 2010a;56:1456-1462.

Assay and Time of Dose Administration	Ticagrelor		p-value	Clopidogrel		p-value
	No PPI (n=25)	PPI (n=12)		No PPI (n=19)	PPI (n=13)	
Maximum response (LTA) to 20 µM ADP (%)						
Before maintenance dose	35±14	37±14	0.59	45±15	56±10	0.04
2-4 h after maintenance dose	27±9	29±12	0.68	39±15	55±15	0.007
Final response (LTA) to 5 µM ADP (%)						
Before maintenance dose	5±8	9±9	0.21	13±11	25±21	0.054
2-4 h after maintenance dose	2±4	3±3	0.73	7±8	23±22	0.013
VerifyNow P2Y12 (PRU)						
Before maintenance dose	74±61	92±116	0.56	181±64	262±76	0.005
2-4 h after maintenance dose	31±34	32±29	0.98	151±70	247±99	0.005
VASP PRI (%)						
Before maintenance dose	25±20	31±19	0.43	53±25	59±18	0.47
2-4 h after maintenance dose	13±13	18±11	0.32	47±24	58±20	0.23

ADP = adenosine diphosphate; LTA = light transmittance aggregometry; PPI = proton pump inhibitor; PRI = platelet reactivity index; PRU = platelet reaction units; VASP = vasodilator-stimulated phosphoprotein.

No additional safety results were presented in this substudy.

Phase II Studies

Bliden KP, Tantry US, Storey RF, et al. The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: combined analysis of the ONSET/OFFSET and RESPOND studies. *Am Heart J*. 2011;162(1):160-165.

Study dates: The study consisted of a subset of patients enrolled in the ONSET/OFFSET study or the RESPOND study. Subjects in the ONSET/OFFSET study were enrolled between October 2007 and March 2009 (Gurbel et al, 2009). Subjects in the RESPOND study were assessed for clopidogrel responsiveness between May 19, 2008 and March 25, 2009 (Gurbel et al, 2010b).

Study location: The ONSET/OFFSET study was conducted at 8 institutions in the United States and the United Kingdom (Gurbel et al, 2009). The RESPOND study was conducted at 10 centers in North American and Europe (Gurbel et al, 2010b).

Study objectives: To compare the prevalence of high platelet reactivity (HPR) in patients randomized to ticagrelor and clopidogrel in the ONSET/OFFSET and RESPOND studies (Bliden et al, 2011).

Study design:

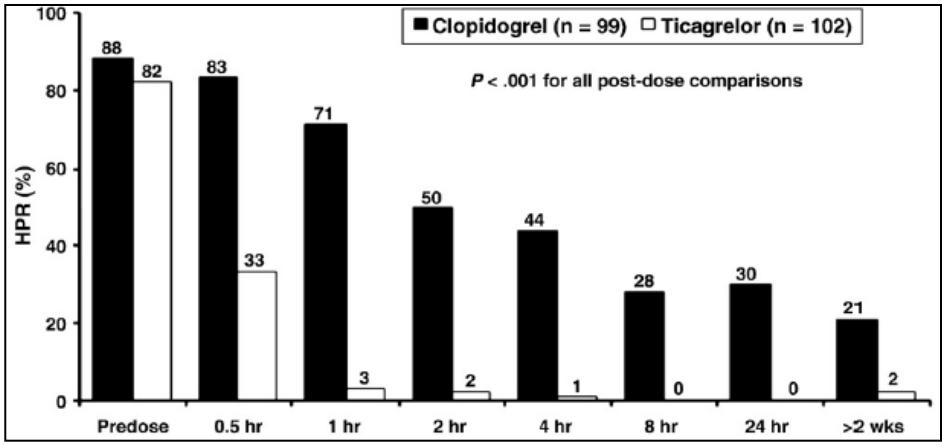
- A planned subanalysis of pooled data from the ONSET/OFFSET and RESPOND studies.
- Platelet function was assessed in 209 patients (ticagrelor [n=106] and clopidogrel [n=103]) using LTA, VerifyNow, and VASP-phosphorylation.

HPR results:

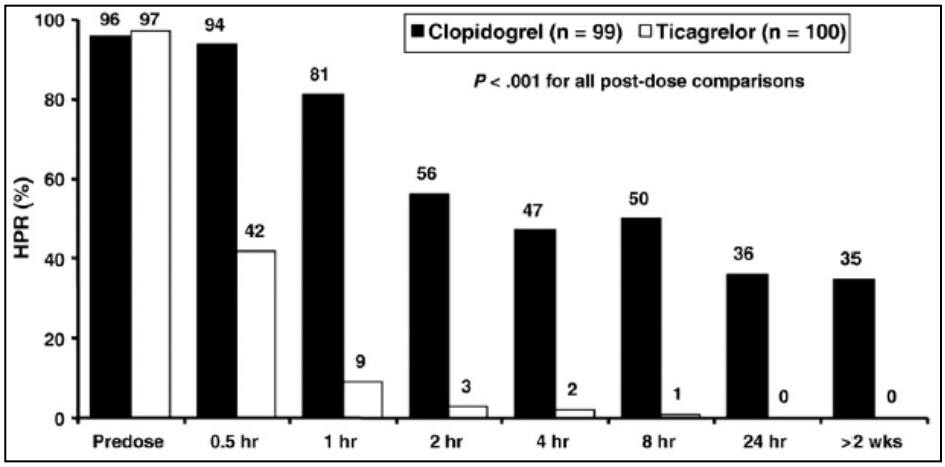
- Ticagrelor was associated with a significantly lower prevalence of HPR versus clopidogrel at 2, 4, 8, and 24 hours, and ≥2 weeks post-dose ($p<0.0001$ for all post-dose comparisons as measured by all assays).
- Thirty minutes after the LD, prevalence of HPR (based on LTA) was 33% with ticagrelor and 83% with clopidogrel. After 1 hour, 97% of ticagrelor-treated patients were below HPR predefined cutoff points of HPR; whereas, 44% of clopidogrel-treated patients demonstrated HPR up to 4 hours after the LD.
- During the maintenance phase, the prevalence of HPR remained high in clopidogrel group (21%) and lower in the ticagrelor group (2%).
- HRP at 24 hours after the last maintenance dose was greater in clopidogrel-treated patients (LTA: 21% vs. 2%; VerifyNow: 35% vs. 0%; VASP-phosphorylation: 65% vs. 5%; $p<0.001$ for all comparisons) compared to ticagrelor-treated patients.
- The prevalence of HPR was similar between ticagrelor- and clopidogrel-treated patients at 48 hours after the last maintenance dose; however, it was higher at 72 hours and 120 hours with ticagrelor compared to clopidogrel as measured by LTA (60% vs. 45% and 80% vs. 66%, respectively; $p<0.05$ for both comparisons).
- This information is depicted in the following figure.

FIGURE 5-1: Prevalence of HPR Measured by LTA (ADP 20 µM), VerifyNow, and VASP phosphorylation[a]

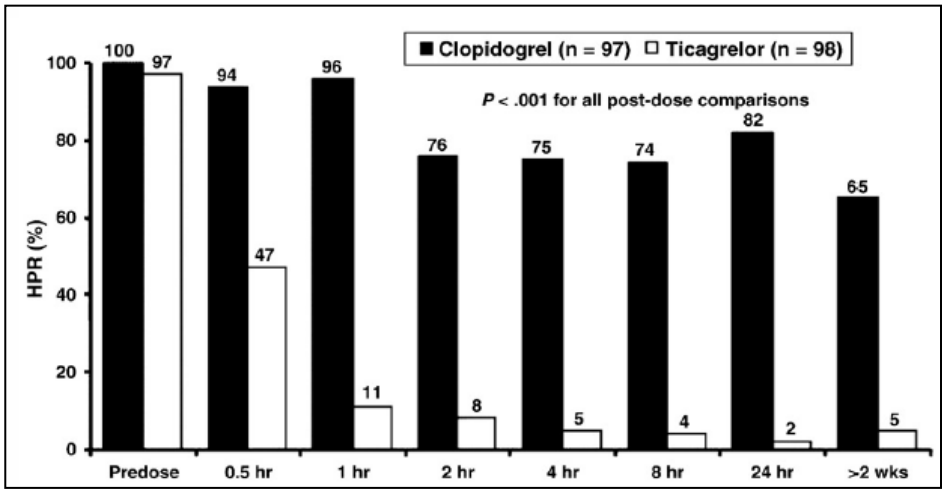
LTA (ADP 20 µM/L)



VerifyNow®



VASP Phosphorylation



ADP = adenosine diphosphate; HPR = high platelet reactivity; LTA = light transmittance aggregometry; VASP = vasodilator-stimulated phosphoprotein. [a]This figure is a copyright- protected work. Unless you have the permission of the copyright owner, or a license from an appropriate authorized licensing body, you may not copy, store in any electronic medium or otherwise reproduce or resell any of the content, even for internal purposes, except as may be allowed by law.

Safety Results:

- No safety data was presented in this planned subanalysis.

Storey RF, Bliden K, Patil SB, et al. Earlier recovery of platelet function after treatment cessation in ticagrelor-treated patients compared to clopidogrel high responders [abstract and poster]. Presented at: European Society of Cardiology Congress; August 28-September 1, 2010; Stockholm, Sweden. *Eur Heart J.* 2010f;31(abs suppl):389. Abs P2313.

Study dates: This subanalysis was a part of the ONSET/OFFSET study. Subjects in the ONSET/OFFSET study were enrolled between October 2007 and March 2009 (Gurbel et al, 2009).

Study locations: The ONSET/OFFSET study was conducted at 8 institutions in the United States and the United Kingdom.

Study objective: To evaluate the time to recovery of platelet function after discontinuation of ticagrelor and clopidogrel in patients with a high response on treatment (Storey et al, 2010f).

Study design: ONSET/OFFSET was a Phase II multicenter, randomized, double-blind, double-dummy, parallel-group study to determine the onset and offset of the antiplatelet effect of ticagrelor compared to high-LD clopidogrel and placebo in patients with stable CAD treated with ASA (N=123) (Gurbel et al, 2009).

Inclusion/exclusion criteria: For the inclusion and exclusion criteria of the ONSET/OFFSET study, see the earlier summary of the study by Gurbel et al (2010a).

Treatment arms/dosing:

- **Initial LD (Day 1):**
  - TCG 180 mg x 1, or
  - CLP 600 mg x 1, or
  - Placebo

- **Maintenance:** TCG 90 mg or placebo in the evening on Day 1, followed by:
  - TCG 90 mg BID (n=57), or
  - CLP 75 mg QD (n=54), or
  - Placebo (n=12) for 6 weeks.

- All patients received ASA 75-100 mg QD.

Endpoints:

- IPA was measured by LTA at various times after administration of the last dose. A high response was defined as IPA >75% (ADP 20 µM, final extent) at 4 hours postdose, <120 PRU at 8 hours postdose, and PRI <50% at 8 hours postdose.

- VerifyNow $P2Y_{12}$ and VASP assays were also conducted at various time points.

Results:

- Thirty-nine patients in the ticagrelor group and 17 patients in the clopidogrel group had IPA >75% at 4 hours postdose. The rate of platelet recovery was faster with ticagrelor between 4 and 48 hours versus clopidogrel; mean IPA was significantly lower with ticagrelor at all time points between 48 and 168 hours versus clopidogrel.

- The rate of offset of antiplatelet activity, estimated by the slope of the IPA curve between 4 and 72 hours postdose, was greater with ticagrelor versus clopidogrel (–1.11 vs. –0.67 IPA %/hour, $p<0.0001$).

- Similar patterns of recovery of platelet function were noted with the VerifyNow $P2Y_{12}$ assay and VASP phosphorylation assay.

Tantry US, Bliden KP, Wei C, et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. *Circ Cardiovasc Genet.* 2010; 3:556-566.

Study dates: The study consisted of a subset of patients enrolled in the ONSET/OFFSET study or the RESPOND study. Subjects in the ONSET/OFFSET study were enrolled between October 2007 and March 2009 (Gurbel et al, 2009). Subjects in the RESPOND study were assessed for clopidogrel responsiveness between May 19, 2008 and March 25, 2009 (Gurbel et al, 2010b).

Study location: The ONSET/OFFSET study was conducted at 8 institutions in the United States and the United Kingdom (Gurbel et al, 2009). The RESPOND study was conducted at 10 centers in North American and Europe (Gurbel et al, 2010b).

Study objectives: To determine the effect of genotypically predicted CYP2C19 metabolizer status on platelet reactivity of ticagrelor versus clopidogrel from the ONSET/OFFSET and RESPOND studies and to compare the platelet reactivity of treatments within specific genotypes

Study design:

- Pooled analysis using data from the RESPOND study (a Phase II, multicenter, randomized, double-blind, double-dummy, 2-way crossover study) and the ONSET/OFFSET study (a Phase II, double-blind, double-dummy, parallel group study)

- Participation in the genetic substudy was voluntary and separate from informed consent provided for the main studies.

- 174 patients (ticagrelor, n=92; clopidogrel, n=82) enrolled in the ONSET/OFFSET and RESPOND studies underwent genotyping.

- Genotyping was performed for the following:
    - CYP2C19 LOF alleles *2, *3, *4, *5, *6, *7, *8
    - CYP2C19 GOF allele *17
    - ABCB1

- Platelet function data were categorized based on metabolizer status (Group I), LOF (Group II) and GOF carrier status (Group III), and ABCB1 genotype.

- Platelet function was measured by aggregometry (ADP 5 and 20 µM/L), VerifyNow $P2Y_{12}$ assay, and VASP phosphorylation assay at predose, 8 hours postdose, and during maintenance treatment.

Inclusion/exclusion criteria:
Inclusion criteria for the ONSET/OFFSET study were the following (Gurbel et al, 2009).

- Age ≥18 years
- Stable CAD
- ASA 75-100 mg/day

Exclusion criteria for the ONSET/OFFSET study were the following.

- History of ACS in prior 12 months
- Any indication for antithrombotic therapy
- Congestive heart failure
- Left ventricular ejection fraction <35%
- FEV_1 or FVC below the lower limit of normal
- Bleeding diathesis
- Severe pulmonary disease
- Pregnancy
- Smoker
- Treatment with moderate or strong P450 3A inhibitors, substrates or strong P450 3A inducers

- Platelets <100,000/mm^3
- Hemoglobin <10 g/dL
- Hemoglobin A_{1c} ≥10%
- History of drug addiction or alcohol abuse in past 2 years
- Need for NSAID
- Creatinine clearance (CrCL) <30 mL/min

Inclusion criteria for the RESPOND study were the following (Gurbel et al, 2010b).
- Stable CAD
- ASA 75-100 mg QD
- Age ≥18 years

Exclusion criteria for the RESPOND study were the following.
- History of ACS within past 12 months
- History of bleeding diathesis or severe pulmonary disease
- Pregnancy
- Tobacco >1 pack per day
- Concomitant therapy within 14 days: strong CYP3A inhibitors or inducers, antithrombotic therapy other than ASA
- NSAID use
- Platelets <100,000 mm^3
- Hemoglobin <10 g/dL
- Hemoglobin A_{1c} ≥10%
- CrCL <30 mL/min
- History of drug addiction or alcohol abuse in past 2 years

Treatment arms/dosing: Patients received either ticagrelor 90 mg BID or clopidogrel 75 mg QD as maintenance therapy. All patients received 75-100 mg ASA daily. See earlier summaries of the ONSET/OFFSET study (Gurbel et al, 2009) and RESPOND study (Gurbel et al, 2010b) for additional details regarding dosing and treatment arms.

Results:
- Both treatment groups had similar demographics and baseline medications, with the exceptions that more patients with hypertension and more patients treated with dihydropyridine derivatives were in the ticagrelor group.

- Both treatments were well balanced in relation to genotype frequencies with the exception that the ticagrelor group had more intermediate metabolizers, and all patients with the *17/*17 genotype were in the ticagrelor group (see following table).

TABLE 5-7: Genotype Frequencies. Adapted from *Circ Cardiovasc Genet.* 2010;3:558.

	Ticagrelor n (%) n=92	**Clopidogrel n (%) n=82**	**p-value**
Group I			
Ultrarapid metabolizer (ultrarapid + rapid heterozygous)	27 (29)	28 (34)	0.37
Extensive metabolizer (extensive)	28 (30)	31 (38)	0.27
Intermediate metabolizer, (intermediate + poor/rapid heterozygous)	35 (38)	20 (24)	0.05
Poor metabolizer (poor)	2 (2)	3 (4)	0.43
Group II[a]			
LOF carrier (intermediate + poor/rapid heterozygous + poor)	37 (40)	23 (28)	0.10
LOF noncarrier (extensive + ultrarapid + rapid heterozygous)	55 (60)	59 (72)	0.10
Group III			
GOF carrier (ultrarapid + rapid heterozygous)	27 (29)	28 (34)	0.48
EM (extensive)	28 (30)	31 (38)	0.27
LOF carrier (intermediate + poor/rapid heterozygous)	37 (40)	23 (28)	0.10
ABCB1 expression			
C/C (high expression)	30 (33)	21 (26)	0.31
C/T (intermediate expression)	43 (47)	40 (49)	0.79
T/T (low expression)	19 (21)	21 (26)	0.44

EM = extensive metabolizer = *1/*1, Wt/Wt; GOF = gain of function; Intermediate metabolizer = *1/*2-*8, Wt/LOF; LOF = loss of function; poor metabolizer = *2-*8/*2-*8, LOF/LOF; poor/rapid heterozygous = *2-8/*17, LOF/GOF; rapid heterozygous = *1/*17, Wt/GOF; ultrarapid = *17/*17, GOF/GOF; Wt = wild type allele. [a]EMs and LOF carriers in groups I and II are the same.

Effect on Platelet Function

- In patients treated with ASA alone, there was no significant influence of genotypes on platelet function.
- ABCB1 genotype did not influence platelet function before or during therapy with ticagrelor or clopidogrel.
- Patients treated with ticagrelor had significantly ($p \leq 0.0016$) lower platelet function as measured by all assays than patients treated with clopidogrel among all CYP 2C19 genotypes studied with the exception of poor metabolizers due to small patient numbers (n=5) having wide confidence intervals in the data.
- Within treatment groups, there was no influence of genotype on platelet function in the ticagrelor group either postloading or during maintenance treatment.
- In the clopidogrel group, the influence of genotype on platelet function as measured by Verify Now $P2Y_{12}$ was noted postloading (p=0.019 among different metabolizers; p=0.01 between LOF carriers and LOF noncarriers; p=0.28 among GOF, LOF, and extensive metabolizers).
- The influence of genotype was more evident during maintenance therapy with clopidogrel as measured by VerifyNow $P2Y_{12}$ assay (p=0.006 among different metabolizers; p=0.002 between LOF carriers and LOF noncarriers; p=0.007 among GOF, LOF, and extensive metabolizers).
- During maintenance therapy, ticagrelor was associated with significant lower platelet function as measured by all assays in *1/*1, *1/*2, *1/*17, and *2/*17 diplotypes ($p \leq 0.009$).
- In clopidogrel-treated patients, there was a significant influence of diplotype status on platelet function as measured by VerifyNow $P2Y_{12}$ assay and a trend towards 20 µM/L ADP-induced aggregation and VASP phosphorylation ($p \leq 0.006$).

Husted S, Storey RF, Harrington RA, et al. Changes in inflammatory biomarkers in patients treated with ticagrelor or clopidogrel. *Clin Cardiol*. 2010;33:206-212.

Study dates: Dates for this substudy of the DISPERSE-2 trial were not reported in this article.

Study locations: One hundred fifty-two sites in 14 countries participated in the DISPERSE-2 trial (Cannon et al, 2007).

Objective: To compare ticagrelor plus ASA with clopidogrel plus ASA for effects on the following inflammatory biomarkers: C-reactive protein (CRP), soluble CD40 ligand (sCD40L), myeloperoxidase (MPO), and interleukin-6 (IL-6) (Husted et al, 2010).

Study design:
- Analysis of the DISPERSE-2 trial, a Phase II randomized, double-blind, double-dummy, multicenter trial
- Inflammatory markers—CRP, sCD40L, MPO, and IL-6—were analyzed at baseline (Day 1, randomization, predose), prior to hospital discharge (Days 2-4), and 4 weeks.

Inclusion/exclusion criteria: Inclusion criteria reported by Husted et al (2010) were the following:
- Hospitalization for NSTE-ACS in the past 48 hrs
- Ischemic symptoms at rest ≥10 min
- Biochemical marker evidence of MI or ECG evidence of ischemia.

Exclusion criteria were not reported by Husted et al (2010). Key exclusion criteria for DISPERSE-2 were the following:
- ST segment elevation lasting at least 20 minutes
- More than 48 hours from onset of symptoms
- PCI or index event resulting from PCI within 48 hours before randomization,
- No significant coronary stenosis detected by angiography, and/or
- Conditions associated with an increased risk of bleeding (eg, GI bleeding within the previous 6 months, hemorrhagic disorder) (Cannon et al, 2007).

Treatment arms/dosing:
- 990 patients who were hospitalized for NSTE-ACS were randomized to treatment and were included in the assessment of inflammatory biomarkers.
- Patients received one of the following treatments for up to 12 weeks:
  - Ticagrelor 90 mg BID (half of the patients received a LD of 270 mg), n=334,
  - Ticagrelor 180 mg BID (half of the patients received a LD of 270 mg), n=323, or
  - Clopidogrel (clopidogrel-naive: 300 mg LD, then 75 mg QD; clopidogrel-pretreated: 75 mg QD), n=327.
- Standard medical and interventional treatment for ACS, including ASA at an initial dose of up to 325 mg followed by 75-100 mg QD, with or without a GP IIb/IIIa inhibitor.

Results:
- No significant differences between treatment groups were found for any of the inflammatory markers studied at any of the time points measured (baseline, hospital discharge, and 4 weeks).
- CRP levels were elevated from baseline to discharge and decreased from baseline to 4 weeks in all groups.
- IL-6 levels were unchanged from baseline to discharge and decreased from baseline to 4 weeks in all groups.
- MPO levels showed little change from baseline and were slightly lower at discharge and 4 weeks.
- sCD40L levels showed little change from baseline and were slightly lower at discharge but similar to baseline at 4 weeks.

Husted SE, Burbel P, Storey RF, et al. Pharmacokinetics and pharmacodynamics of ticagrelor in patients with stable coronary artery disease [abstract]. *Circulation*. 2009;120:S1102. Abs 5494.

Study dates and location: Dates and location were not provided in the meeting abstract.

Study objective: To evaluate the PK and PD of ticagrelor in patients with stable CAD

Study design: An analysis of PK from a multicenter, randomized, double-blind trial (ONSET-OFFSET) and a 2-way crossover trial (RESPOND) (Gurbel et al, 2009; Gurbel et al, 2010b).

Inclusion/exclusion criteria: These criteria were not provided in the meeting abstract (Husted et al, 2009).

Treatment arms/dosing:

- Patients in the ONSET-OFFSET trial under treatment with ASA (75-100 mg) were randomized to ticagrelor 90 mg BID following a 180 mg LD (n=57); clopidogrel 75 mg QD following a 600 mg LD (n=54); or placebo (n=12) for 6 weeks.

- Patients in the RESPOND trial with stable CAD treated with ASA (75-100 mg daily) and classified as clopidogrel nonresponders (n=41) or clopidogrel responders (n=57) were randomized to 14 days of treatment with clopidogrel 75 mg QD following a 600 mg LD; or ticagrelor 90 mg BID following a 180 mg LD, with no washout between treatments.

Results:

- In the ONSET-OFFSET trial, the C_{max}, t_{max}, and $t_{1/2}$ values of ticagrelor 90 mg BID were 733 ng/mL, 2 hours, and 10.2 hours for ticagrelor, respectively; and 210.3 ng/mL, 2.1 hours, and 12.8 hours for AR-C124910XX, respectively. These values were comparable to those seen previously in healthy subjects. Trough plasma levels of ticagrelor were 304.6 ng/mL, and trough plasma levels of AR-C124910XX were 120.7 ng/mL.

- In the RESPOND trial, the mean C_{max} and area under the curve from 0 to infinity ($AUC_{0-\infty}$) of ticagrelor following 2 weeks of maintenance doses of 90 mg BID were similar between clopidogrel responders treated with 75 mg QD (724.2 ng/mL and 3982.7 ng·h/mL, respectively) and clopidogrel nonresponders treated with 75 mg QD (764.4 ng/mL and 3985.2 ng·h/mL, respectively). The PK of ticagrelor was not affected when ticagrelor was administered 24 hours post-clopidogrel dosing.

- No safety results were reported in the abstract.

Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral $P2Y_{12}$ receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:1852-1856.

Storey RF, Husted S, Harrington RA, et al. Supplementary appendix. *J Am Coll Cardiol*. 2007;50:1852-1856. Available at: http://content.onlinejacc.org/content/vol10/issue2007/images/data/j.jacc.2007.07.058/DC1/jac13279app.doc. Accessed April 29, 2010.

Study dates: Dates were not provided in the article.

Study locations: This substudy of the DISPERSE-2 trial was conducted at selected centers.

Objective: To compare the antiplatelet effects of ticagrelor and clopidogrel and assess the effects of ticagrelor in clopidogrel-pretreated patients.

Study design: Substudy of the DISPERSE-2 trial (Cannon et al, 2007), a Phase II, randomized, double-blind, double-dummy trial

Inclusion/exclusion criteria:

Inclusion:
- Ages 18 years or older
- Admission to the hospital within the prior 48 hours for ischemic chest pain associated with ECG changes that indicated ischemia but no sustained ST-segment elevation, and/or abnormally increased cardiac markers

Exclusion:
- PCI within the prior 48 hours
- Increased bleeding risk
- Thrombolytic therapy within the prior 7 days
- Treatment with strong CYP3A4 inhibitors or 3A4 substrates with a narrow therapeutic index
- Treatment with GP IIb/IIa inhibitors within prior 24 hours or 7 days (abciximab), unfractionated heparin within 24 hours, or dipyridamole within 24 hours of randomization

Treatment arms/dosing:
- 91 patients with NSTE-ACS treated with baseline ASA were enrolled in this substudy, of whom 89 received study medication and had evaluable data.

- Patients received the one of the following treatments for up to 12 weeks:
  - Ticagrelor 90 mg BID (half of the patients received a LD of 270 mg),
  - Ticagrelor 180 mg BID (half of the patients received a LD of 270 mg), or
  - Clopidogrel (clopidogrel-naive: 300 mg LD, then 75 mg QD; clopidogrel-pretreated: 75 mg QD).

- Patients undergoing PCI within 48 hours after randomization could be given an additional 300 mg LD of clopidogrel (or placebo) at the discretion of the treating physician.

- All patients received ASA 325 mg as a LD, followed by 75 to 100 mg once daily.

Endpoints: ADP-induced platelet aggregation as assessed by optical aggregometry on Day 1 and at 4-week intervals. PK parameters were also measured (Storey et al, 2007).

Results:

IPA:
Clopidogrel-naive patients

- Ticagrelor inhibited platelet aggregation dose-dependently. IPA levels for all ticagrelor doses were greater than the maximum level of inhibition seen after the clopidogrel LD; it took 4 hours to achieve the maximum IPA ($p<0.001$ for all ticagrelor groups vs. clopidogrel at 4 hours, final aggregation response).

- IPA by ticagrelor remained stable at 4 weeks, with the most consistent response being seen with ticagrelor 180 mg twice daily.

Clopidogrel-pretreated patients:

- Both doses of ticagrelor inhibited platelet function in a dose-dependent manner, irrespective of previous treatment with clopidogrel.

PK results:
Clopidogrel-naive patients

- Mean levels of ticagrelor in clopidogrel-naive patients were highest at the 2-hour time point, whereas mean levels of AR-C124910XX peaked at 2 to 4 hours with levels 2- to 5-fold lower versus levels of ticagrelor.

Clopidogrel-pretreated patients
The levels of ticagrelor and AR-C124910XX were similar in the clopidogrel-pretreated patients, indicating that the PK of ticagrelor is not affected by clopidogrel pretreatment.

Safety results: There was no safety analysis in this substudy.

5.1.1.2 Published and Unpublished Economic Studies for Labeled and Off-label Indications

Costs and Health Outcomes Based on the Study of PLATelet Inhibition and Patient Outcomes (PLATO)

In House Data. Study of Platelet Inhibition and Patient Outcomes (PLATO) Health Economics Substudy. AstraZeneca LP, 2011.

Funding: AstraZeneca

Key Findings:

- Ticagrelor treatment resulted in use of fewer medical resources, including, all-cause inpatient bed days and CV interventions (PCIs, and CABGs) than clopidogrel treatment in the PLATO study.

- Ticagrelor treatment compared with clopidogrel resulted in lower medical care costs in patients eligible for 12-month follow-up and the overall PLATO population. The cost savings was driven by fewer all-cause inpatient bed days and CV interventions.

- In patients taking low-dose ASA in the PLATO study, similar results of fewer resources and medical care cost savings were observed.

Study Design: The substudy was planned in conjunction with the PLATO study to evaluate within-trial resource use patterns and medical care costs of index hospitalization visit and the follow-up period after index hospitalization for patients treated with either ticagrelor or clopidogrel.

Endpoints: The endpoints assessed were resource utilization (all-cause inpatient bed days, investigations, CV interventions, and bleeding related utilization) and medical care cost over 12 months.

Methods: Resource use data was collected on all patients from all sites of the PLATO trial. Medication utilization and associated costs were excluded. Resource utilization were categorized as all-cause inpatient bed days (general ward, intensive coronary care); investigations (stress test, ECGs, CT scans, MRI, etc); CV interventions (revascularization procedures, defibrillators, etc); and bleeding-related utilization (RBC units, re-operation due to bleeding postCABG, etc). The unit costs of resource use items were obtained from a single health care setting in the southeastern US. The cost of medical care was calculated by multiplying the individual resource use item with the unit cost. Twelve-month costs were estimated to the full PLATO population and for patients eligible for 12-month follow-up. The medical care costs for ticagrelor and clopidogrel were estimated at 1, 6, 9, and 12 months for patients who were eligible for a 12-month follow-up.

Because ticagrelor is recommended for use only with low-dose ASA, resource use results and costs were also estimated for a low-dose ASA cohort (defined as patients who were on a maintenance ASA dose of ≤100 mg per day).

Sample Characteristics: This substudy included all 18,624 patients (clopidogrel, n=9291; ticagrelor, n=9333) from the PLATO study population. Of these, 10,686 patients (clopidogrel, n=5339; ticagrelor, n=5347) were eligible for 12-month follow-up. A total of 15,439 patients (clopidogrel, n=7733; ticagrelor, n=7706) were taking low-dose ASA; 8941 patients (clopidogrel, n=4481; ticagrelor, n=4460) were eligible for a 12-month follow-up.

Results: Resource use patterns observed in the PLATO study showed ticagrelor patients to have fewer all-cause inpatient bed days (mean difference of 0.21 per patient), fewer PCIs (mean difference of 0.01 per patient), and fewer CABGs (mean difference of 0.01 per patient) than clopidogrel patients (see the following table).

TABLE 5-8: Per-patient Resource Use Patterns Observed in the PLATO Study.[a]

	Index Hospitalization			After Index Hospitalization			Total Study Period		
Resource use item	**CLP n=9291**	**TCG n=9333**	**Difference (CLP-TCG)**	**CLP n=9291**	**TCG n=9333**	**Difference (CLP-TCG)**	**CLP n=9291**	**TCG n=9333**	**Difference (CLP-TCG)**
Bed days	8.06	7.97	**0.09**	4.37	4.24	**0.13**	12.42	12.21	**0.21**
Stress test	0.06	0.06	**0.00**	0.18	0.18	**-0.01**	0.24	0.24	**0.00**
Echocardiography	0.65	0.64	**0.01**	0.30	0.30	**0.00**	0.95	0.95	**0.01**
Coronary angiography	0.85	0.84	**0.01**	0.19	0.18	**0.01**	1.04	1.03	**0.02**
Other investigations[b]	0.07	0.07	**0.00**	0.13	0.14	**-0.01**	0.20	0.21	**-0.01**
PCI	0.65	0.64	**0.01**	0.13	0.12	**0.01**	0.78	0.76	**0.01**
Bare metal stent	0.60	0.59	**0.01**	0.09	0.08	**0.01**	0.68	0.67	**0.02**
Drug-eluting stent	0.29	0.27	**0.02**	0.08	0.07	**0.01**	0.37	0.34	**0.02**
CABG	0.06	0.05	**0.00**	0.05	0.05	**0.00**	0.10	0.10	**0.01**
Other interventions[c]	0.03	0.03	**0.00**	0.01	0.01	**0.00**	0.04	0.04	**0.00**
Units of blood products[d]	0.33	0.32	**0.01**	0.21	0.22	**0.00**	0.54	0.53	**0.01**

CABG = coronary artery bypass graft; CLP = clopidogrel; PCI = percutaneous coronary intervention; TCG = ticagrelor. [a]The table excludes events which occur prior to randomization or after the last expected visit date. [b]Other investigations includes myocardial scintigraphy, electrophysiology study, Holter study, ventilation/perfusion scan, pulmonary angiography, computer tomography of head/brain, spinal, chest, helical, abdomen, and extremity, Magnetic Resonance Imaging of head/brain, spinal, chest, abdomen, and extremity. [c]Other interventions includes pacemaker, implantable cardiac defibrillator, intra-aortic balloon pump, and left ventricular assist device. [d]Units of blood products includes units of packed red blood cells, units of whole blood, units of fresh frozen plasma, and units of platelets.

Treatment with ticagrelor resulted in estimated savings of $1019 (95% CI: -101, 2138) per patient in cumulative medical care costs compared with treatment with clopidogrel in patients eligible for 12-month follow-up. The estimated savings in cumulative medical care costs was $815 (95% CI: -4, 1633) per patients with the use of ticagrelor compared with clopidogrel in all patients included in the PLATO study. In both populations, the cost savings was driven by fewer all-cause inpatient bed days and CV interventions (see the following table).

TABLE 5-9: Medical Care Costs.

	Patients Eligible for 12-month Follow-up				Full PLATO Cohort			
Resource use	**Clopidogrel (n=5339)**	**Ticagrelor (n=5347)**	**Difference (95% CI)**	**p-value**	**Clopidogrel (n=9291)**	**Ticagrelor (n=9333)**	**Difference (95% CI)**	**p-value**
Bed days	$25,402	$24,615	$787 (-200, 1774)	0.118	$24,373	$23,847	$526 (-193, 1245)	0.151
Investigations	$2763	$2738	$26 (-37, 88)	0.42	$2716	$2683	$33 (13, 80)	0.155
CV Interventions	$6808	$6606	$202 (-42, 446)	0.105	$6754	$6500	$254 (68, 440)	0.007
Bleeding Related	$178	$174	$4 (-43, 50)	0.873	$158	$157	$2 (-29, 32)	0.921
Total Costs	**$35,152**	**$34,133**	**$1,019 (-101, 2138)**	**0.075**	**$34,001**	**$33,187**	**$815 (-4, 1633)**	**0.051**

Low-dose ASA Cohort

In the low-dose ASA cohort, ticagrelor was associated with fewer all-cause inpatient bed days (mean difference of 0.33 per patient) and fewer CABG procedures (mean difference of 0.01 per patient compared to clopidogrel use (see the following table).

TABLE 5-10: Per-patient Resource Use Patterns Observed in the PLATO Study—Low-dose ASA Cohort.[a]

	Index Hospitalization			After Index Hospitalization			Total Study Period		
Resource use item	**Clopidogrel (n=7706)**	**Ticagrelor (n=7733)**	**Difference (Clopidogrel-Ticagrelor)**	**Clopidogrel (n=7706)**	**Ticagrelor (n=7733)**	**Difference (Clopidogrel-Ticagrelor)**	**Clopidogrel (n=7706)**	**Ticagrelor (n=7733)**	**Difference (Clopidogrel-Ticagrelor)**
Bed days	8.23	8.11	**0.12**	4.55	4.34	**0.22**	12.78	12.45	**0.33**
Stress test	0.07	0.06	**0.01**	0.19	0.20	**-0.01**	0.26	0.26	**0.00**
Echocardiography	0.67	0.66	**0.01**	0.31	0.32	**0.00**	0.98	0.98	**0.00**
Coronary angiography	0.84	0.84	**0.01**	0.19	0.20	**0.00**	1.03	1.03	**0.00**
Other investigations[b]	0.07	0.07	**0.00**	0.12	0.13	**-0.01**	0.19	0.20	**-0.01**
PCI	0.65	0.65	**0.00**	0.13	0.13	**0.01**	0.78	0.78	**0.00**
Bare metal stent	0.62	0.61	**0.01**	0.09	0.08	**0.00**	0.71	0.69	**0.02**
Drug-eluting stent	0.27	0.26	**0.01**	0.08	0.07	**0.00**	0.34	0.33	**0.01**
CABG	0.05	0.04	**0.01**	0.05	0.05	**0.00**	0.10	0.09	**0.01**
Other interventions[c]	0.03	0.02	**0.00**	0.01	0.01	**0.00**	0.04	0.03	**0.00**
Units of blood products[d]	0.25	0.21	**0.04**	0.20	0.21	**-0.01**	0.46	0.43	**0.03**

[a]The table excludes events which occurred prior to randomization or after the last expected visit date. [b]Other investigations included myocardial scintigraphy, electrophysiology study, Holter study, ventilation/perfusion scan, pulmonary angiography, computer tomography of head/brain, spinal, chest, helical, abdomen, and extremity, Magnetic Resonance Imaging of head/brain, spinal, chest, abdomen, and extremity. [c]Other interventions included pacemaker, implantable cardiac defibrillator, intra-aortic balloon pump, and left ventricular assist device. [d]Units of blood products includes units of packed red blood cells, units of whole blood, units of fresh frozen plasma, and units of platelets.

The estimated savings in cumulative medical care cost was $1143 (95% CI: -84, 2369) per patient with the use of ticagrelor compared with clopidogrel in low-dose ASA patients eligible for 12-month follow-up. The estimated savings in cumulative medical care cost was $1002 (95% CI: 108, 1895) per patients with the use of ticagrelor compared with clopidogrel in all low-dose ASA patients included in the PLATO study. In both populations, the cost savings was also driven by fewer all-cause inpatient bed days and CV interventions (see the following table).

TABLE 5-11: Medical Care Costs—Low-dose ASA Cohort.

	Patients Eligible for 12-month Follow-up				Full PLATO Cohort			
Resource use	**Clopidogrel (n=4460)**	**Ticagrelor (n=4481)**	**Difference (95% CI)**	**p-value**	**Clopidogrel (n=7706)**	**Ticagrelor (n=7733)**	**Difference**	**p-value**
Bed days	$25,986	$25,077	$909 (-176, 1995)	0.101	$24,953	$24,211	$741 (-45, 1528)	0.065
Investigations	$2768	$2759	$9 (-59, 77)	0.793	$2714	$2708	$6 (-44, 57)	0.806
CV Interventions	$6699	$6468	$231 (-20, 482)	0.072	$6611	$6368	$243 (47, 439)	0.015
Bleeding Related	$146	$152	$-6 (-52, 40)	0.796	$137	$126	$11 (-20, 42)	0.487
Total Costs	**$35,598**	**$34,455**	**$1143 (-84, 2369)**	**0.068**	**$34,415**	**$33,414**	**$1002 (108, 1895)**	**0.028**

The cumulative median medical care costs were lower with ticagrelor treatment during the entire 12-month period in both the PLATO study population eligible for 12-month follow-up and in the low-dose ASA cohort eligible for 12-month follow-up.

Conclusion: Treatment with ticagrelor resulted in fewer resource use and lower medical care costs compared with clopidogrel treatment, for both the overall PLATO study population and in a subgroup of patients taking ASA ≤100 mg/day. The 12-month cost per patient was on average $1019 lower with ticagrelor than with clopidogrel and $1143 lower in the low-dose ASA cohort in patients eligible for a 12-month follow-up.

Economic Burden of ACS in a Managed Care Setting

Etemad LR, McCollam PL. Total first-year costs of acute coronary syndrome in a managed care setting. *J Manag Care Pharm*. 2005;11:300-306.

Funding: Eli Lilly and Company

Study dates: July 1, 1999-June 30, 2001

Key findings:

- Total health care costs for the study population were $22,529 per patient or $2312 per patient-month.
- Of the expenses incurred, the majority (93%) were medical expenses with pharmacy accounting for 7%; a total of 71% of expenditures were attributed to hospitalizations.
- An estimated 93% of patients were hospitalized at least once during the study period and 51% of patients had at least 1 revascularization procedure.

Study design: This was a retrospective, descriptive analysis using administrative claims data (medical, pharmacy, eligibility) from a large managed care organization (MCO) to estimate the total cost of health care utilization, for the health plan and patient, in a 12-month period following newly onset ACS.

Endpoints: The endpoints of the analysis included the rate of hospitalization, the rate of revascularization, the pattern of drug therapy use, and the total health services utilization and cost.

Methods: Data was obtained from a large MCO (>3.65 million members) with commercial, preferred-provider organization model health plans. Medicare Advantage plans were not included. Patients aged ≥18 years with an *International Classification of Diseases, 9th Edition/Revision* (ICD-9) code for MI or UA and had at least 6 months of continuous eligibility prior to their index event and did not have any claims with an ACS diagnosis during the baseline period were included in the analysis. The index event was indicated as the first emergency room visit or hospitalization for MI or UA. ICD-9 codes were used to identify patient comorbidities and revascularization procedures during the study period. Revascularization procedures included PTCA, stent implantation, or CABG. Medication use was obtained from pharmacy claims data for nonstatin lipid-lowering therapy, HMG Co-A reductase inhibitors, beta-blockers, ACE-I, ARBs, calcium channel blockers, and clopidogrel. The data period included 12 months of study data plus 6 months of baseline data prior to entry in the study. Baseline data was reviewed for a previous ACS diagnosis or medication use. Comorbidities were captured at any point in the study period, including baseline and follow-up periods. Health care costs were calculated from the amount paid by the health plan and the co-pay and deductibles paid by the patient.

Sample characteristics: A total of 13,731 patients met study inclusion and represented 0.4% of the managed care members. The patient population yielded at total of 133,814 months of follow-up with a mean of 9.75 months. The majority of the study population was aged 45 to 64 years (73%) and male (68%). UA was present in 51.7% of the patients and the majority of patients (85%) entered the study through an inpatient stay.

Results: A full 12-month follow-up was completed by 64% of patients. The average number of comorbidities was 12.7. Hypertension and lipid disorders were each indicated in 73% of patients, while 30% had a diagnosis of diabetes mellitus and 30% has a diagnosis of alcohol and drug abuse.

Rate of hospitalization: Nearly all patients (93%) had at least 1 hospitalization during the study period. The mean number of hospital days per patient-month was 0.65. A total of 3,641 patients (26.5%) had more than 1 hospitalization, and there were 6,770 hospitalizations after the index date.

Rate of revascularization: Revascularization procedures were completed in 51% of patients with the majority receiving the procedure on their index event date (69%). Stents were the majority of procedures completed (34%), followed by CABG (14%) and PTCA (2%).

Pattern of drug therapy use: Most patients received a cholesterol-lowering medication during follow-up (55.9% received a statin, 10.3% a non-statin cholesterol medication). A total of 58.4% of patients received a beta-blocker, 37.6% received an ACE-I, 6.9% received an ARB, and 24.2% received a calcium channel blocker. In addition, 36% of patients received

clopidogrel during the follow-up period, with the majority (95%) newly initiating therapy. The mean length of clopidogrel therapy was 92 days.

Health services utilization costs: Total health care costs for the study population was approximately $309 million. With 13,731 patients treated for 133,814 months, this was estimated to be $22,529 per patient or $2312 per patient-month. Hospitalizations accounted for 71% or $221 million of the overall costs. Office/outpatient visits accounted for $37 million during the study period with cardiologist visits being most prevalent (24%). ER visits contributed $12 million during the study period. Pharmacy costs contributed $23 million during the study period (see the following table).

TABLE 5-12: Health Services Cost in the Follow-Up Period. Adapted from *J Manag Care Pharm*. 2005;11:300-306.

Indicator	Entire Population (13,731 patients)	Per Patient (9.75 months)	Per Patient Per Month (133,814 months)
Hospitalizations	$220,606,503	$16,066	$1649
Nursing home stays	$863,686	$62.90	$6.45
Lab visits	$11,388,230	$829.38	$85.11
Emergency room visits	$11,904,762	$867.00	$88.97
Office/outpatient visits	$37,247,855	$2712.68	$278.36
Surgery center visits	$2,640,653	$192.31	$19.73
"Other" medical visits	$1,529,464	$111.39	$11.43
Total cost in follow-up	**$309,338,394**	**$22,528.47**	**$2,311.70**

The index event was attributed with more than 50% of the medical costs or $168 million. Patients with an inpatient index event had a higher mean cost than those with an ER index event. Similarly, patients with an acute MI had higher mean costs than those with a diagnosis of UA (see the following table).

TABLE 5-13: Comparison of Index Events and Diagnosis by Total Cost and Length of Stay. Adapted from *J Manag Care Pharm*. 2005;11:300-306.

Indicator	Mean Cost (Standard Deviation)
Index event: hospitalization	$14,254 (19,307)
Index event: emergency room visit	$488 (976)
Diagnosis: unstable angina	$8101 (12,501)
Diagnosis: acute myocardial infarction	$14,254 (19,307)

Conclusion: The authors concluded that managed care patients with newly onset ACS incur a substantial cost in the following year, and there are opportunities to improve medication therapy after an acute ACS event.

Berenson K, Ogbonnaya A, Casciano R, et al. Economic consequences of ACS-related rehospitalizations in the US. *Curr Med Res Opin.* 2010;26:329-336.

Funding: sanofi-aventis and Bristol-Myers Squibb

Study dates: 2002 to 2007

Key findings:

- The mean charges for ACS rehospitalization were approximately $52,000.
- ACS-related procedures, comorbidities, and increased length of stay (LOS) were the main factors in the increased charges.
- Older patients with previous chronic comorbidities and interventions at hospitalization were likely to have an increased LOS.

Study design: Two retrospective observational studies were conducted to determine the cost of recurrent ACS-related hospitalizations following new onset of ACS in 2 managed care populations.

Endpoints: The primary endpoint was the direct charges related to ACS rehospitalization, defined as a result of ACS (UA or MI), or an ACS-related procedure (CABG, stent insertion, or PCI). The predictors of increased ACS charges and LOS were also determined.

Methods: Two databases were used for data generation, PharMetrics and Henry Ford Health System (HFHS). PharMetrics is a large (over 85 health plans, 2.4 billion healthcare services) database that represents the national managed care population in the US. HFHS is a smaller, regional health system in the Detroit area that includes information from over 2.5 million provider visits. Patients with a diagnosis of UA or MI, or an ACS-related procedure as identified by ICD-9 procedure or diagnosis code or Current Procedural Terminology (CPT) code for MI, UA, CABG, stent placement, or PCI were included in the analysis. The date of UA/MI diagnosis or ACS-related procedure was defined as the ACS index date. Patients aged <18 years or enrolled in the health plan for less than 6 months prior to the index date to ensure that the patient had not experienced a prior ACS event were excluded from the analysis. Patients were followed for 2 years.

Health encounter records and insurance claims were used to estimate medical care resource utilization. Recurrent ACS-related hospitalization charges for medical care services, medications, supplies and other resources recorded in the administrative billing records were used as a measure of cost. Charges for only the first rehospitalization related to ACS were assessed. The mean and median charge was computed and stratified by age group and by type of ACS rehospitalization. All charges were adjusted to 2007 US dollars using the medical care component of the Consumer Price Index (CPI).

Sample Characteristics: HFHS hospitals accounted for 11,266 patients compared to 97,177 patients in the PharMetrics group. These 2 groups differed in several baseline demographics due to the HFHS patients being older (55% >65 years vs. 34% >65 years) which resulted in higher percentages of patients with disease in every studied category except dyslipidemia. These included CHF, angina, dysrhythmia, hypertension, renal insufficiency, and COPD. This age difference may have also contributed to a difference in time to rehospitalization, which was 118 days for HFHS compared with 205 days for PharMetrics.

Results: A total of 3,588 (32%) of patients in the HFHS analysis had at least 1 ACS rehospitalization compared with 32,578 (34%) of patients in the PharMetics analysis. The mean time to rehospitalization following index ACS hospitalization discharge for the HFHS and PharMetric populations was 118.44 (182.97) days and 205.16 (319.12), respectively.

Direct charges related to ACS rehospitalization: Mean charges for all ages and over or under age 65 were similar for both databases for ACS-related rehospitalization (see the following table). Both databases showed extra mean charges of approximately $52,000 for rehospitalizations.

TABLE 5-14: Mean Hospitalization Charges for ACS Patients. Adapted from *Curr Med Res Opin.* 2010;26:329-336.

	Data source	Mean Charge (SD)	Median Charge
All ages	HFHS PharMetrics	$52,619 (61,628) $52,352 (35,712)	$32,222 $78,062
Age <65 years	HFHS PharMetrics	$50,813 (58,217) $51,455 (36,839)	$32,411 $63,262
Age ≥65 years	HFHS PharMetrics	$54,119 (64,300) $54,136 (32,945)	$32,019 $101,233

Predictors of increased ACS charges: Inpatient procedures, acute MI, and increased LOS were the main causes of the increased charges of $52,000 for both databases (see the following table). A few differences in the predictors were seen when the LOS was removed. Predictors of decreased charges varied among the databases.

TABLE 5-15: Multivariate Analysis: Predictors of Increased ACS-related Charges. Adapted from *Curr Med Res Opin.* 2010;26:329-336.

Predictor of increased ACS related charge	HFHS with LOS Beta Coefficient (Difference in Charges, $)	HFHS without LOS Beta Coefficient (Difference in Charges, $)	PharMetrics with LOS Beta Coefficient (Difference in Charges, $)	PharMetrics without LOS Beta Coefficient (Difference in Charges, $)
Age	-$5645 (p<0.0001)	NS	-$229 (p<0.0001)	-$73 (p=0.0569)
Male	NS	-$2993 (p=0.0891)	$3130 (p=0.0001)	$1530 (p=0.0857)
LOS	$6759 (p<0.0001)	NS	$4223 (p=0.0001)	NS
CABG-rehospitalization	$56,385(p<0.0001)	$93,580 (p<0.0001)	$74,642 (p<0.0001)	$95,291 (p<0.0001)
CABG-index hospitalization	NS	$12,952 (p=0.0004)	$4215 (p=0.0157)	$8367 (p<0.0001)
Stent-rehospitalization	$8199 (p=0.0046)	NS	$31,363 (p<0.0001)	$26,271 (p<0.0001)
Stent-index hospitalization	$2688 (p=0.0779)	NS	-$1553 (p=0.0559)	-$2669 (p=0.0023)
PCI rehospitalization	$16,844 (p<0.0001)	$13,920 (p<0.0001)	$22,379 (p<0.0001)	$20,750 (p<0.0001)
PCI-index hospitalization	—	—	$3706 (p=0.0233)	NS
Acute MI-rehospitalization	NS	$18,862 (p<0.0001)	$6,511 (p<0.0001)	$13,612 (p<0.0001)
UA-rehospitalization	-$5761(p<0.0001)	-$8392 (p<0.0001)	$5132 (p<0.0001)	$4375 (p<0.0001)
History of peripheral vascular disease	NS	NS	-$1567 (p=0.512)	-$3569 (p<0.0001)
History of angina	-$3545 (p=0.0119)	-$3844 (p=0.0697)	-$1567 (p=0.0512)	-$3569 (p<0.0001)
History of stroke	NS	$5393 (p=0.0498)	-$3998 (p=0.0003)	$2247 (p=0.0632)
History of diabetes	NS	$4894 (p=0.0106)	NS	$2096 (p=0.0146)
History of hypertension	-$3643 (p=0.0052)	-$3793 (p=0.0538)	$3616 (p=0.0071)	$3405 (p=0.0197)
History of hypotension	NS	$9553 (p=0.0456)	$4882 (p<0.0001)	$7659 (p<0.0001)
History of dyslipidemia	$2929 (p=0.0225)	NS	$6994 (p<0.0001)	NS
History of renal disease	NS	$5566 (p=0.0731)	$5641 (p<0.0001)	$14,335 (p<0.0001)
History of chronic obstructive pulmonary disease	-$2621 (p=0.093)	NS	$1640 (p=0.0541)	$2869 (p=0.0019)
History of congestive health failure	—	—	$3231 (p=0.0004)	$7433 (p<0.0001)
History of other cardiac dysfunction	—	—	$4336 (p<0.0001)	$5842 (p<0.0001)
History of prior bleed	$2675 (p=0.0734)	$7186 (p=0.0026)	$3679 (p<0.0001)	$5607 (p<0.0001)

CABG = coronary artery bypass graft; LOS = length of stay; MI = myocardial infarction; NS = not significantly different; PCI = percutaneous coronary intervention; UA = unstable angina.

Predictors of increased LOS: Older patients with previous chronic comorbidities and interventions at hospitalization were all likely to have an increased LOS. Stents at rehospitalization and less severe disease such as dyslipidemia were predictors of shorter LOS.

Conclusion: Substantial costs result from ACS rehospitalizations. ACS-related procedures and co-morbidities, resulting in increased LOS, are the main contributors to the increased charges.

Menzin J, Wygant G, Hauch O, et al. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. *Curr Med Res Opin.* 2008;24:461-468.

Funding: AstraZeneca

Study dates: 2000 to 2003

Key findings:

- 21.1% of patients with an initial ACS-related hospitalization were readmitted within 1 year.
- The average cost of the first rehospitalization was $28,637.
- The strongest factors predicting rehospitalization were the presence of comorbidities, ACS listed as primary diagnosis at the initial hospitalization, and age.

Study design: This was a retrospective single-cohort study using administrative claims data for patients with ACS to determine the characteristics of hospitalized ACS patients, factors associated with readmission, and the costs associated with ACS over the course of 1 year.

Endpoints: The primary endpoint was the duration and cost of the initial hospitalization and the rate and cost of rehospitalization. Additional endpoints assessed included factors associated with a greater likelihood of rehospitalization and the cost of care for ACS over the course of 1 year.

Methods: This study utilized data from the Medstat MarketScan Commercial Claims and Encounters database. This database collects data from employers, health plans, and government organizations covering over 4 million patients in the US. All patients included in this study were enrolled in employer-sponsored health plans, and complete information regarding their inpatient, outpatient, and prescription claims was available for analysis.

Patients who were hospitalized between January 2001 and December 2002 with a diagnosis of ACS (ICD-9-CM codes 410.xx and 411.1) were included in the analysis. Patients had to be at least 35 years old and had at least 12 months of insurance eligibility prior to the index admission (defined as the first ACS-related hospitalization during the study period). Patients with a hospitalization or medical claim related to ACS in the 12 months prior to the index admission were excluded from the study. Patients were followed for either 1 year following their index admission date or until they disenrolled from the health plan.

Descriptive analyses of patient characteristics were undertaken, including demographics and comorbidities. Analysis of factors related to rehospitalization included those thought to be important predictors including demographics, comorbidities, treatment during the initial hospitalization and prior CV medications. Costs were broken into 3 main categories: ACS-related, all ischemic heart disease (IHD)-related, and all-cause. All costs were adjusted to reflect 2005 US dollars using the Medical Care CPI.

Sample characteristics: A total of 16,321 patients were included in the analysis. The mean age (±SD) was 55.6 (±6.7) years; the cohort was predominantly male (66.7%). Common comorbidities included diabetes without chronic complications (15.4%), chronic pulmonary disease (7.4%), CHF (4.3%), and cerebrovascular disease (3.7%).

Results: Of the patients included in the initial cohort, approximately 1% died during the index hospitalization. The mean LOS was 4.6±6.7 days and the mean cost was $22,921±31,400 per patient. Approximately 46% of patients underwent a revascularization procedure during the initial hospitalization.

Hospital rehospitalization: Of patients who survived the initial admission, 21.1% were readmitted with at least 1 eligible rehospitalization. Of these, 2,591 (16.1%) had 1 IHD-related rehospitalization, 562 (3.5%) had 2 rehospitalizations, and 250 (1.6%) had 3 or more rehospitalizations during the follow-up period. The mean time from initial hospitalization discharge to first rehospitalization was 58.1±78.5 days. During their first rehospitalization, 53% of patients had some type of revascularization including CABG (15.2%), PCI with stent (22.3%) and PCI without stent (13.3%). 2.3% had multiple revascularization procedures performed. The mean cost for the first IHD-related rehospitalization was $28,637±32,972.

Predictors of rehospitalization: The strongest predictors for rehospitalization were found to be the presence of comorbidities, whether or not the initial hospitalization listed ACS as the primary diagnosis, and age (see the following table). Patients who had either CABG surgery or PCI with stent procedure during their initial hospitalization were the least likely to be rehospitalized.

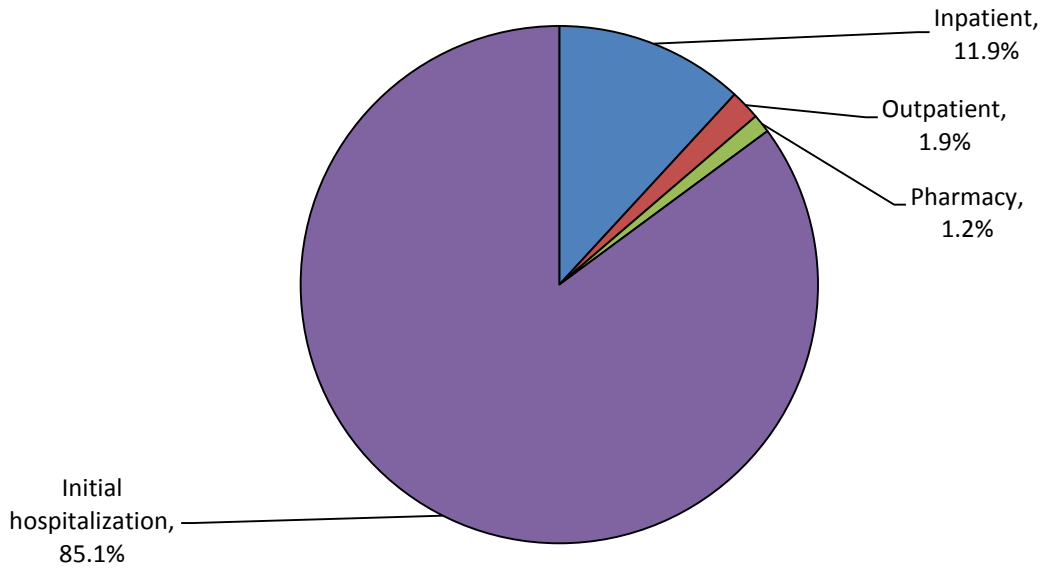
TABLE 5-16: Cox Proportional Hazard Model for the Predictors of IHD-related Rehospitalization. Adapted from *Curr Med Res Opin.* 2010;24:461-468.

Parameter	Hazard Ratio	95% Confidence Interval
Charlson comorbidity index score >1 (vs. 0)	1.53	(1.37, 1.71)
ACS listed as primary diagnosis at initial hospitalization	1.50	(1.40, 1.61)
Age >55 years (vs. <45 years)	1.24	(1.07, 1.44)
Male	1.18	(1.09, 1.27)
CABG during initial hospitalization	0.52	(0.45, 0.59)
PCI with stent during initial hospitalization	0.90	(0.83, 0.97)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

Costs in the year following initial hospitalization: In the year following the initial hospitalization, ACS-related costs averaged $26,931±34,089. The costs were driven by the cost of the initial hospitalization (85.1%), followed by rehospitalization costs (11.9%) (see the following figure). During the first year after hospitalization, 90% of patients were using lipid-lowering, antihypertensive, or antiarrhythmia medications, and 50% of patients were prescribed anticoagulant or antiplatelet medications. Costs peaked in the first 3 months after the initial hospitalization, and decreased over the remaining 12 months. ACS costs accounted for 83% of the total first year IHD-related costs ($32,345±37,899).

FIGURE 5-2: Distribution of Costs 1 Year After ACS Hospitalization. Adapted from *Curr Med Res Opin.* 2010;24:461-468.



Conclusion: Rehospitalization rates in ACS patients are high within the first year. The initial hospitalization and rehospitalization are the most significant factors influencing the cost of care. The main predictors of rehospitalization are the presence of comorbidities, ACS listed as the primary diagnosis at the initial hospitalization, and age.

Rehospitalization Rates, Mortality Rates, and Hospital Costs

Tunceli O, Gandhi S, Bhandary D, et al. Re-hospitalization rates of acute coronary syndrome patients in real-world clinical practice: Observations from a national administrative Claims Database. Poster presented at: International Society Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 21-25, Baltimore, Maryland.

Funding: AstraZeneca

Study Dates: January 2007-May 2010

Key Findings:
- Rehospitalization and mortality rate for ACS patients within 30-days and 12-months post-initial hospitalization discharge in real-world clinical practice is high.
- There is an opportunity to improve clinical and economic outcomes of care with ACS.

Study Design: This was a retrospective, observational medical claims cohort study that assessed the rates of rehospitalization and mortality among patients with ACS in real-world clinical practice within 30 and 365 days of initial hospitalization.

Endpoints: The outcome measures were rehospitalization rates for an ACS-related cause, rehospitalization rates for any reason, and mortality rates within 30 or 365 days post initial hospitalization.

Methods: This cohort study was conducted using administrative medical claims data from the HealthCore Integrated Research Database (HIRD℠). In addition, the Social Security Death Index (SSDI) database was used to determine mortality (all-cause death) following the initial ACS hospitalization. Patients aged ≥18 years with ≥1 medical claim for an inpatient hospitalization for ACS between January 2007 and May 2010 and ≥1 claim for an ACS-related procedure or another diagnosis, and who were continuously enrolled for 12 months prior to the start of the initial ACS hospitalization event were included in the study. All MI patients were also required to have ≥1 day of inpatient stay or discharge status determined as death. Patients with ACS events within 1 year prior to initial hospitalization were excluded from the study.

The number of ACS rehospitalizations and any rehospitalizations within 30 or 365 days post-initial hospitalization were recorded. The mortality rate within 30 and 365 days post-initial hospitalization was determined by the number of patients who died within 30 or 365 days post-initial hospitalization divided by the total number of ACS patients.

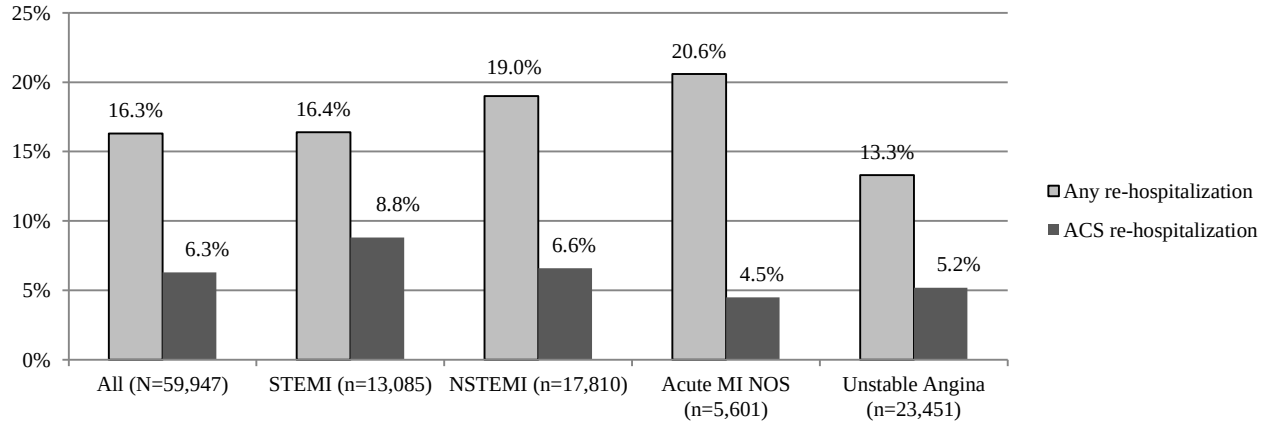
Sample Characteristics: A total of 66,772 patients were eligible for the study and were included in the following cohorts:
- ≥1 STEMI diagnosis and 1 procedure code for MI: 14,511 (21.7%) patients
- ≥1 NSTEMI diagnosis and 1 procedure code for MI: 20,757 (31.1%) patients
- ≥1 not otherwise specified (NOS) diagnosis and 1 procedure code for MI: 7053 (10.6%) patients
- ≥1 UA diagnosis and ≥1 procedure code for UA: 24,451 (36.6%) patients

A greater percentage of the ACS patients were males (60.1%) with the highest percentage (67%) in the STEMI patient cohort. Approximately half (50.1%) of the patients were ≥65 years; in each of the ACS cohorts, the majority of patients were ≥65 years, with the exception of the STEMI cohort (39.4%). A higher proportion of all patients were in the Midwest geographic region and the majority of the patients had a preferred provider organization (PPO) type of health plan. For all ACS patients, the mean length of inpatient hospital stay was 6.41 days, with UA patients having the lowest number of days (4.12 days).

Results:

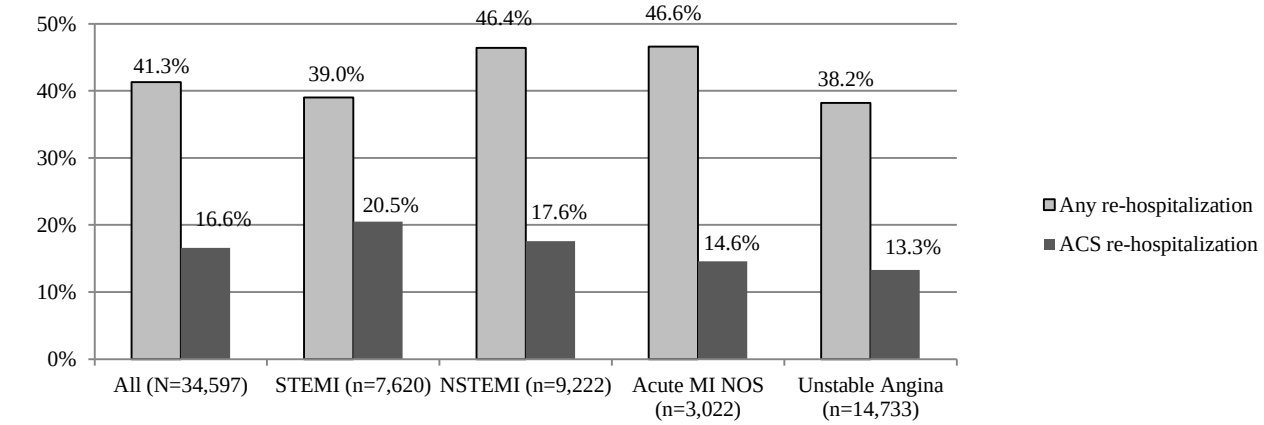
A total of 59,947 patients met the inclusion criteria and the 30-day eligibility requirement and were included in the analysis. As shown in the figure below, the 30-day all-cause rehospitalization rate for all ACS patients was 16.3%, and ranged from 13.3% for (UA) to 20.6% for (MI-NOS) for the individual ACS cohorts (see the following figure). Overall, the rate of ACS-related rehospitalizations was 6.3%. ACS-related rehospitalization rates ranged from 4.5% (MI-NOS) to 8.8% (STEMI) (see the following figure). Rehospitalization trends were similar among patients aged ≥65 years (n=33,502).

FIGURE 5-3: 30-day Rehospitalization Rates Among Patients with ≥30 Days of Eligibility. Adapted from poster presented at ISPOR May 21-25, 2011, Baltimore, Maryland.



A total of 34,597 patients had ≥365 days of eligibility postinitial hospitalization and were included in the 12-month rehospitalization analysis. As shown in the figure below, the 12-month all-cause rehospitalization rate for all ACS patients was 41.3%, and ranged from 38.2% (UA) to 46.6% (MI-NOS). ACS-related rehospitalization rates ranged from 13.3% (UA) to 20.5% (STEMI) (see the following figure). Trends were similar among patients aged ≥65 years.

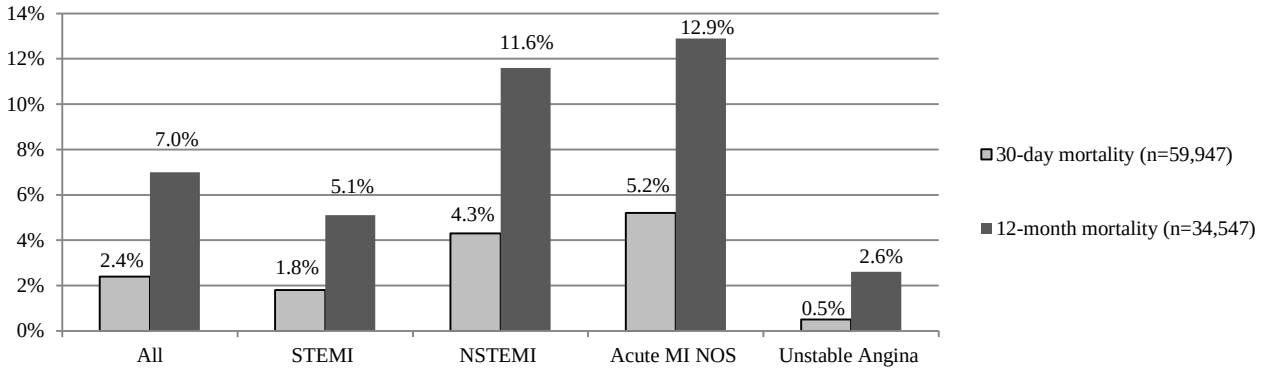
FIGURE 5-4: 12-month Rehospitalization Rates Among Patients with at Least 365 Days of Eligibility. Adapted from poster presented at ISPOR May 21-25, 2011, Baltimore, Maryland.



When the rehospitalization rates were evaluated by the index hospitalization procedure, the 30-day rehospitalization rates ranged from 13.6% after BMS PCI to 17.8% after CABG. The 30-day ACS-related rehospitalization rates ranged from 2.9% after CABG to 8.0% after BMS PCI. Similarly, the 12-month all-cause rehospitalization rates ranged from 37.2% after primary angioplasty without stent to 40.0% after DES, while the ACS-related rehospitalization rates ranged from 9.7% after CABG to approximately 21% after DES and BMS PCI.

Mortality was higher in the NSTEMI and acute MI NOS groups, followed by STEMI and UA groups, in both the 30-day and 12-month data sets (see the following figure). Mortality rates were higher among patients aged ≥65 years but followed a similar trend (30-days mortality rates: STEMI 4.3%, NSTEMI 7.8%, MI-NOS 10.1 %, UA 0.9% and 12-months mortality rates: STEMI 21.5 %, NSTEMI 40.9%, MI-NOS 47.7 %, UA 7.5%).

FIGURE 5-5: 30-day and 12-month Mortality Rates. Adapted from poster presented at ISPOR May 21-25, 2011, Baltimore, Maryland.



Conclusion: The authors concluded that rehospitalization and mortality rate for ACS patients within 30-days and 12-months postindex hospitalization discharge in real-world clinical practice is high, indicating an opportunity to improve the clinical and economic outcomes of care in this patient population. In addition, the use of more effective therapies in ACS patients may improve clinical and economic outcomes.

Hess GP, Bhandary D, Gandhi S, et al. Use of hospital claims data to estimate the clinical and economic burden of ACS re-hospitalizations in real-world clinical practice. Poster presented at: The American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.

Funding: AstraZeneca

Study Dates: January 2007-April 2009

Key Findings:

- Rates of rehospitalization for ACS patients within 30 days and 12 months after the index hospitalization are high.
- The economic burden of rehospitalizations is substantial; the mean per-patient hospital charges for 365-day rehospitalizations were $53,052 (all-cause) and $19,838 (ACS-related); higher charges were seen in NSTEMI and UA patients.

Study Design: This was a retrospective, claims-based cohort study of patients with newly diagnosed ACS to examine inpatient rehospitalization rates and the economic burden of ACS admissions in real-world clinical practices from a hospital perspective.

Endpoints: The outcome measures were ACS-related rehospitalization rates, all-cause rehospitalization rates, and hospitalization charges within 30 or 365 days after the initial hospitalization.

Methods: This cohort study was conducted using SDI databases, including hospital charge detail masters, private practitioner medical claims, pharmacy prescription claims, and consumer insights data. Patients aged ≥18 years with a new case of ACS diagnosed during inpatient hospitalization during the study period who had at least ≥1 year of medical or hospital claims in the preindex period and either ≥1 year of data postindex or who had a recorded mortality postindex were included in the analysis. In addition, patients were required to have ≥6 months of pharmacy claims data preindex and either ≥1 year of data postindex or have a recorded mortality postindex. Patients missing age or gender data and those with a continuing episode of ACS at time of index hospitalization were excluded from the study.

The number of ACS rehospitalizations and all-cause rehospitalizations within 30 or 365 days postinitial hospitalization were recorded. Hospitalization charges incurred during inpatient hospitalizations within 30 days and 365 days after initial hospitalization was also determined.

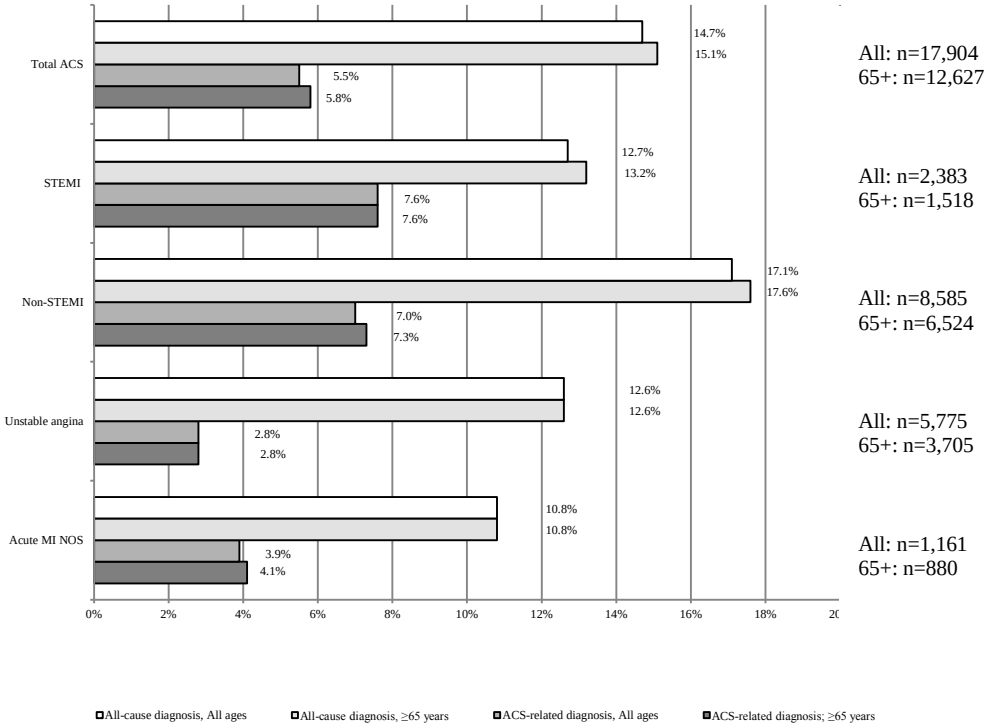
Sample Characteristics: A total of 17,904 patients (13.3% with STEMI, 48% with NSTEMI, 32.3% with UA, and 6.5% with acute MI-NOS) were included in the analysis. The mean age of STEMI patients was 68.4 years; UA patients had a mean age of 68.5 years. NSTEMI and acute MI-NOS patients were both older than STEMI patients, with mean ages of 72.3 years ($p<0.001$) and 72.5 years ($p<0.001$), respectively. A higher proportion of STEMI patients (55%) were males compared to NSTEMI patients (51%, $p<0.001$) and acute MI-NOS patients (52%, $p<0.05$). A similar proportion of UA patients were male (54%). CV risk factors were present in the majority of patients: 78% of NSTEMI, 79% of UA and 82% of acute MI-NOS patients presented with CV risk factors while STEMI patients had a substantially lower rate (66%, $p<0.0001$ compared to each of the other ACS groups). A total of 12,627 (70%) patients were aged ≥65 years (1518 STEMI, 6524 N STEMI, 3705 UA, and 880 acute MI-NOS).

Results:

30-day Rehospitalization Rates and Charges

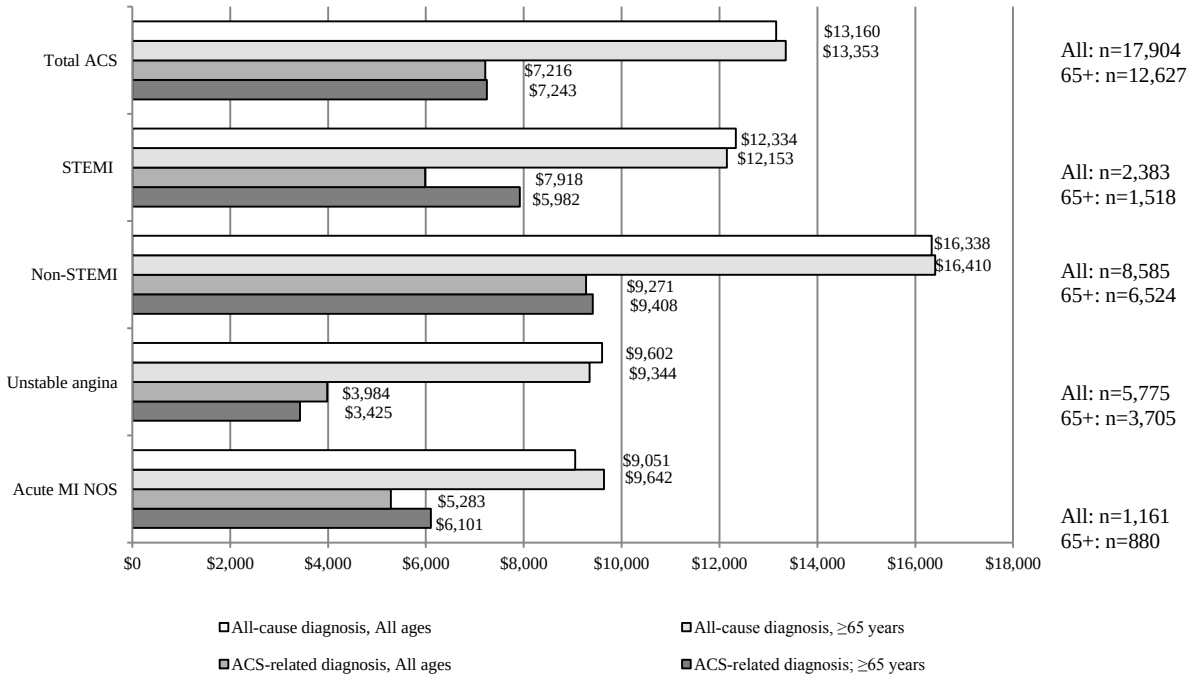
The 30-day all-cause rehospitalization rate was 14.7%; the rate was slightly higher in patients ≥65 years (15.1%). The rate of ACS-related rehospitalization within 30 days was 5.5%, and also slightly higher in patients aged ≥65 years (5.8%). Patients with NSTEMI had a significantly greater rate of all-cause rehospitalizations compared to STEMI (17.1% vs. 12.7%, respectively; $p<0.0001$); however, they had a comparable ACS-related rehospitalization rate to STEMI (7.0% vs. 7.6%, respectively) (see the following figure).

FIGURE 5-6: Percentage of ACS Patients Rehospitalized Within 30 days for Index Discharge. Adapted from poster presented at the American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.



The mean hospital charges for 30-day rehospitalizations among all ACS patients were $13,160 per patient (all-cause) and $7216 per patient (ACS-related). For patients aged ≥65 years, the mean per-patient charges were similar ($13,353 all-cause and $7243 ACS-related). As shown in the following figure, the mean per-patient charges were highest for NSTEMI patients, at $16,338 all-cause and $9271 ACS-related.

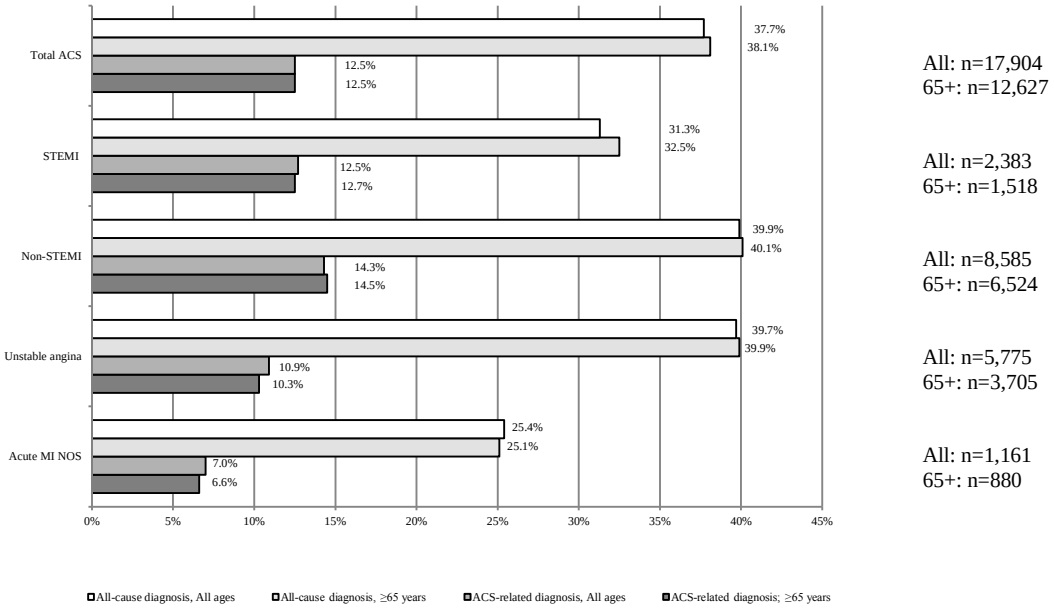
FIGURE 5-7: Mean Per-patient Rehospitalization Charges Within 30 Days Post Index Discharge. Adapted from poster presented at the American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.



365-day Rehospitalization Rates and Charges

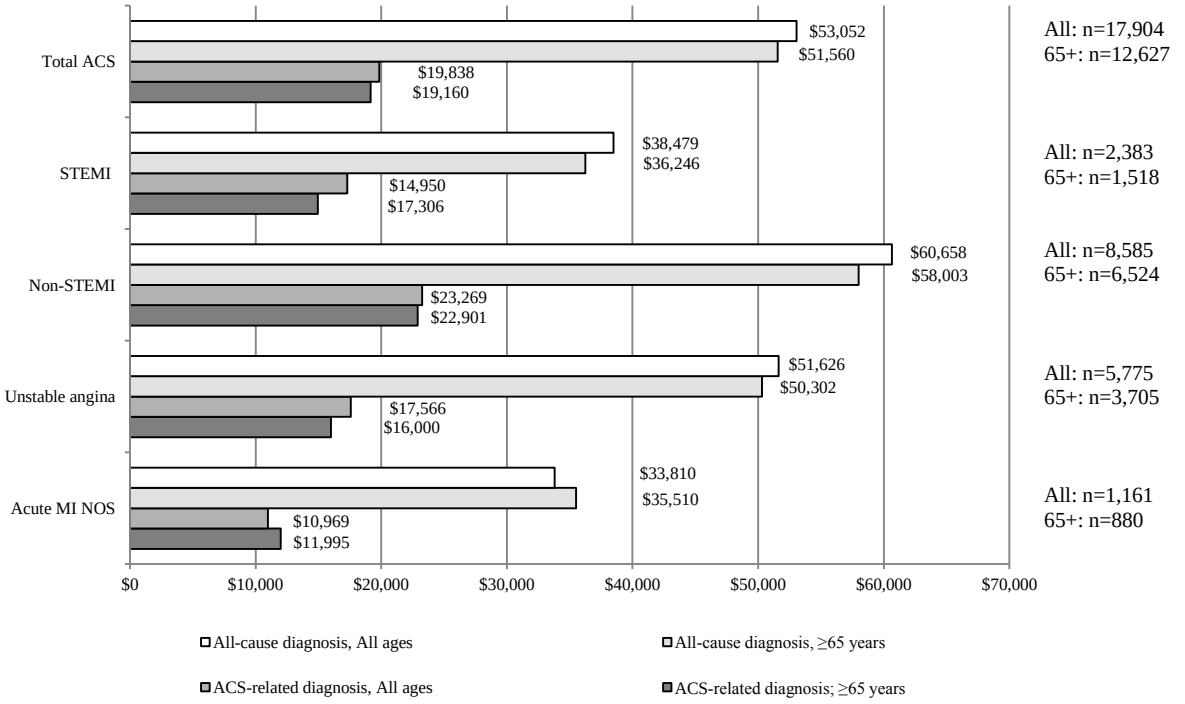
The 12-month all-cause rehospitalization rate was 37.7% among all ACS patients and was slightly higher in patients ≥65 years (38.1%). NSTEMI and UA patients had an 8.6% and 8.4% higher rate of all-cause rehospitalizations than STEMI ($p<0.0001$), while acute MI-NOS patients had a 5.9% lower rate than STEMI ($p=0.0003$). The 12-month ACS-related rehospitalization rate was 12.5% overall and for patients aged ≥65 years (see the following figure).

FIGURE 5-8: Percentage of ACS Patients Rehospitalized Within 365 days for Index Discharge. Adapted from poster presented at the American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.



Overall, the mean per-patient charges for 12-month rehospitalizations were $53,052 all-cause and $19,838 ACS-related. The NSTEMI patients had the highest mean per-patient charges ($60,658 all-cause and $23,269 ACS-related) (see the following figure).

FIGURE 5-9: Per-patient Rehospitalization Charges Within 365 Days Post Index Discharge. Adapted from poster presented at the American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.



Conclusion: The authors concluded that the rates of rehospitalization for ACS patients are high within 30 days and 12 months after the initial hospitalization and result in a substantial economic burden. More effective therapies may provide an opportunity to improve important clinical and economic outcomes in ACS patients and assist in reducing rehospitalizations and associated costs.

Access to Therapy in ACS

Philipson TJ, Mozaffari E, Maclean JR. Pharmacy cost sharing, antiplatelet therapy utilization, and health outcomes for patients with acute coronary syndrome. *Am J Manag Care*. 2010;16:290-297.

Funding: Bristol-Myers Squibb, sanofi-aventis

Study dates: 2002-2005

Key findings: Higher patient cost-sharing results in the following:

- Lower adoption of antiplatelet therapy
- Higher probability of discontinuing antiplatelet therapy
- Increased ACS-related hospitalizations
- Higher costs paid by the health care plans.

Study design: This was a retrospective, longitudinal outcomes study using administrative data for medical and pharmacy claims of patients enrolled at health plans offered by 26 large private employers to examine how cost-sharing for prescription drugs affects compliance with antiplatelet therapy and subsequent health outcomes among patients with ACS.

Endpoints: The endpoint of the study was relationship between health plan cost-sharing and other controlled variables on the independent variables including utilization, antiplatelet therapy adoption and discontinuation, ACS hospitalization, and total expenditures on ACS hospitalizations.

Methods: Patients were identified from a longitudinal database of medical and pharmacy claims linked to benefit design information for a group of large private employers. Patient claims data from 2002 to 2005 were evaluated based on the ICD-9 codes for ACS. The patient sample was further restricted to patients undergoing implantation of 1 or more coronary stents during this period. Patients included in the study did not have a prior hospital admission with an ACS diagnosis and did not receive antiplatelet therapy in the 12 months preceding the first stent implantation. Pharmacy claims data were used to identify the fill date, dosage, and days supplied for all antiplatelet drugs.

To evaluate total drug utilization, adoption was used to define the filling of the antiplatelet outpatient prescription following discharge and adherence was used to define the discontinuation of antiplatelet drug therapy following implantation of the initial stent. ACS hospitalization (hospitalization after stent implantation with ACS diagnosis) was used to compute total medical expenditures for all payers associated with the ACS hospitalization. Cost-sharing was defined as the percentage of total pharmaceutical expenditures paid by the patient. Health plans were further categorized as high and low cost-sharing plans.

Sample characteristics: A total of 14,325 privately insured ACS patients met study inclusion and represented 265 plan years and covered 26 different employers. The majority of the study population was at least 65 years of age (57%) and male (70%).

Results: For the study population, prescriptions for antiplatelet drugs were filled 6.9 times per patient on average during the first year following stent placement. This increased to 9.2 prescriptions per patient during the second year. The coinsurance rate for antiplatelet drugs was lower (17%) than all other drugs (21%) during the study period.

Adoption of antiplatelet therapy over the 40 days after implantation of the index stent and probability of discontinuation: Patients with ACS who had higher coinsurance were less likely to adopt outpatient antiplatelet therapy within the first month after stent implantation and are more likely to discontinue treatment in the first year after stent implantation ($p<0.01$). At 40 days after stent implantation, the estimates for adopting antiplatelet therapy was 90% for low cost-sharing compared with 86% for high cost-sharing ($p<0.01$). In addition, the probability of discontinuing antiplatelet therapy in high cost-sharing and low cost-sharing health plans both increased over time. However, from 3 to 12 months after stent implantation, there was approximately a 1.8% greater chance of discontinuing therapy in the high cost-share group ($p<0.01$).

Number of ACS hospitalizations per patient: In both the cost-sharing health plans, rehospitalizations per patient for the 12 months after stent implantation increased over time. The groups started to separate after 3 months and at 12 months there

were 0.47 hospitalizations per patient in the high cost-share group compared to 0.4 in the low cost-sharing group (p<0.01). Note that these values do not represent the probability of rehospitalization because some patients will have multiple ACS rehospitalizations in the year.

Annual expenditures for ACS rehospitalizations between the low and high cost-sharing plans: First-year expenditures on ACS hospitalizations were increased in the high cost-sharing group by $2,796 compared to the low cost-sharing plan, which was shared by the patient and the insurance plan. Taking into account the insurance company saves $1,577 in pharmaceutical costs by passing those costs to the patients, the high cost-sharing plan still lost $603 per patient due to the higher hospitalization costs. The following table gives the estimated annual expenditures for ACS rehospitalizations between the low and high cost-sharing plans.

TABLE 5-17: Predicted Annual Expenditures on ACS Hospitalizations in High Cost-sharing and Low Cost-sharing Health Plans During the First and Second Years after Stent Implementation. Adapted from *Am J Manag Care.* 2010;16:290-297.

	Low Cost-Sharing Plans (Mean $)	High Cost-Sharing Plans (Mean $)	Difference
ACS Hospitalization Expenditures—First Year	$7361	$10,157	38% (p<0.01)
ACS Hospitalization Expenditures—Second Year	$5146	$4904	-4.7% (p=0.82)

Conclusion: High cost-sharing insurance plans, meant to be a cost-savings mechanism for health care costs, actually increases costs through decreased adoption of proper therapy, increased discontinuation of therapy by the patient, and increased hospitalizations.

Medication Adherence in ACS Patients

Hess G, Bhandary D, Fonseca E, et al. Adherence to medications with once-a day (QD) and twice-a-day (BID) dosing formulations in acute coronary syndrome (ACS) patients. Poster presented at: International Society Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 21-25, 2011, Baltimore, Maryland.

Funding: AstraZeneca

Study Dates: January 2007-April 2009

Key Findings:

- There were no differences in adherence between once daily and twice daily dosing formulations over a 12-month period in patients with ACS.
- All measures of adherence, including persistency, days on therapy, and refill compliance rate, were lower than ideal.
- Results indicate potential opportunities to improve adherence with chronic therapies in ACS patients.

Study Design: This was a retrospective, claims-based cohort study evaluating adherence with once daily and twice daily regimens of chronic medications in newly diagnosed ACS patients.

Endpoints: The endpoints assessed were persistency with therapy (defined as the percentage of patients without therapy lapse of >30 days between fills); the number of days on therapy; average number of prescriptions filled for the study drugs; and refill compliance.

Methods: Patient data were obtained using United States prescription claims and mortality databases. Newly diagnosed ACS patients aged ≥18 years during inpatient hospitalization that were dispensed a prescription for carvedilol and/or metformin within 60 days of discharge from the ACS inpatient hospitalization were included in the study. Patients were required to have pharmacy activity for ≥1 year postdischarge or have a recorded postdischarge death. Patients had to also have filled ≥2 prescriptions for the same drug and formulation to be included in the refill compliance analysis.

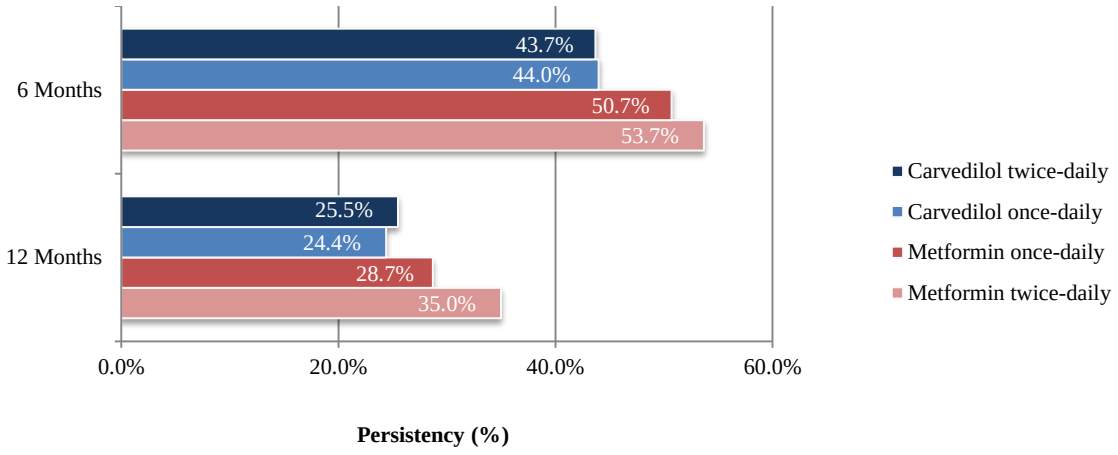
The chronic medications evaluated were carvedilol (generic or branded) twice daily, carvedilol once daily, and metformin once daily (identified by NDC number). Because NDC codes are not specific for twice daily metformin, dispensed quantity divided by days supply was used to identify patients in the metformin twice daily cohort. Patients who switched to another dosing frequency or discontinued therapy were categorized as discontinued. Refill compliance was defined and calculated using the medication possession ratio (MPR), determined as the total days supply dispensed divided by calendar days between first and last prescription in the cohort period.

Sample Characteristics: A total of 2254 carvedilol patients and 750 metformin patients were included in the study. The 168 carvedilol once daily patients were compared with 2086 carvedilol twice daily patients and 136 metformin once daily patients were compared with 614 metformin twice daily patients. Patients within each drug group comparison were statistically no different from each other in mean age and gender. The mean age was between 66 and 70 years and the majority of patients were males.

Results:

At 6 months, 44.0% of carvedilol once daily were persistent compared with 43.7% of the carvedilol twice daily patients (p=0.934). At 12 months, persistency was still not significantly different between carvedilol once daily and twice daily (24.4% vs. 25.5%, respectively; p=0.753) (see the following figure). Similar results were seen with metformin as slightly over half of both once daily and twice daily patients were persistent at 6 months (50.7% vs. 53.7%, p=0.524) and less than a third at 12 months (28.7% vs. 35.0%, p=0.158).

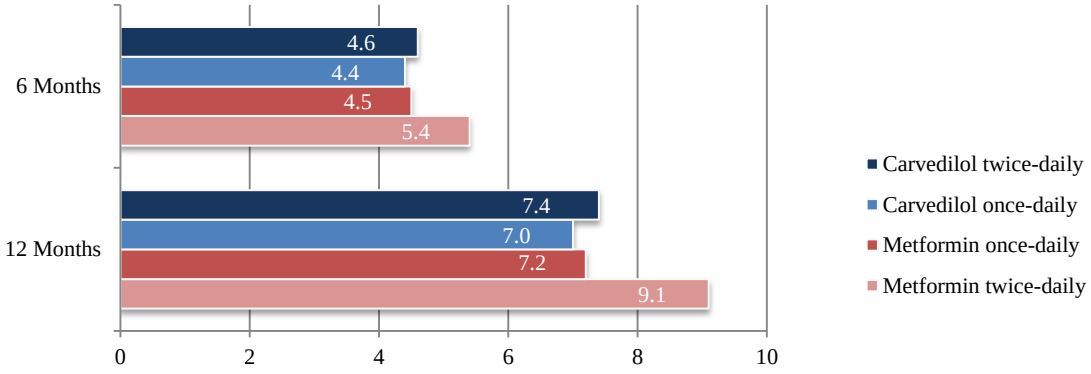
FIGURE 5-10: Persistency Among Once Daily Versus Twice Daily Patients After Discharge from ACS Inpatient Hospitalization. Adapted from poster presented at ISPOR May 21-25, 2011, Baltimore, Maryland.



During the 6-month period, carvedilol once daily and twice daily patients were on therapy approximately 67% of days (120.5 vs. 121.9 days, p=0.766). Similar results were seen over the 12-month period (196.7 vs. 203.0 days, p=0.526). Patients on metformin twice daily were on therapy for 75% of the 6-month period which was significantly higher than once daily patients (136.2 vs. 123.6 days, p=0.013). At 12 months, metformin twice daily patients were on therapy for approximately 65% of the period as compared to 56% of days for once daily patients (237.7 vs. 206.1 days, p=0.005).

The average number of prescriptions filled was not significantly different between patients receiving carvedilol once daily and twice daily during the 6-month or 12-month period. On average, patients receiving metformin twice daily filled 1 more prescription than metformin once daily during 6 months (5.4 vs. 4.5, p=0.0002) and 2 more prescriptions than metformin once daily during 12 months (9.1 vs. 7.2, p<0.0001) (see the following figure).

FIGURE 5-11: Average Number of Prescriptions with 6 Months and 12 Months After Discharge from ACS Inpatient Hospitalization. Adapted from poster presented at ISPOR May 21-25, 2011, Baltimore, Maryland.



Carvedilol once daily patients had a 4% greater refill compliance rate at 12 months compared to twice daily patients (84.2% vs. 80.7%, p=0.026). Refill compliance of metformin once daily versus twice daily was statistically no different (77.6% vs. 81.6%, p=0.066).

Conclusion: The authors concluded that over a 12-month period, the adherence measures generally showed no differences between once daily and twice daily dosing formulations of chronic medications in ACS patients. However, all measures showed a lower than ideal adherence and refill compliance with prescribed medications.

Consequences of Not Discontinuing Clopidogrel Use Prior to Surgery

Berger JS, Frye CB, Harshaw Q, et al. Impact ofclopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol.* 2008;52:1693-1701.

Harshaw Q, Wygant GD, Hauch O, et al. Pharmacoeconomic analysis of bleeding complications and reoperation costs in patients with ACS receiving clopidogrel who require CABG surgery. Poster presented at: American Heart Association 9th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke; May 1-2, 2008; Baltimore, MD.

Funding: AstraZeneca

Study dates: 2004-2007

Key findings:

- Use of clopidogrel within 5 days of CABG surgery resulted in increased rates of major bleeding and reoperation and longer LOS.
- Higher total costs, direct costs, and overhead costs which could have been avoided were associated with the use of clopidogrel use within 5 days of CABG surgery.
- The higher rate of reoperation was a key driver in increased total costs.

Study design: This was a protocol-driven, retrospective cohort analysis using data collected from randomly selected ACS patients undergoing CABG in 14 US hospitals who received clopidogrel and those who were either clopidogrel-naive or had not used clopidogrel within 5 days of undergoing surgery.

Endpoints: The primary endpoints were the rate of reoperation, major bleeding, and LOS. Secondary endpoints included reoperation for bleeding complication; percentages of nonlife-threatening bleeding; death, reinfarction, or stroke; number of transfusions given, and ICU and postsurgical LOS. A pharmacoeconomic subanalysis also assessed total costs, direct costs, and overhead costs.

Methods: Teaching and nonteaching hospitals as well as hospitals performing the CABG procedure on-pump or off-pump, which conducted at least 350 CABG procedures annually, were included in the analysis. Case records of eligible patients treated between January 2004 and December 2006 were used to complete case report forms including demographic, clinical, and financial data. Patients aged ≥30 years who presented with ACS between January 2004 and December 2006, underwent CABG during the index hospitalization, and, if complete records were not available from a referring hospital, remained at 1 hospital for management were included in the study. Patients with end-stage renal disease, other open-heart procedures along with CABG, a bleeding disorder, lost to follow-up within 30 days after CABG surgery, death unrelated to cardiac condition or surgery, surgery not performed within 7 days of the index hospitalization or angiography for ACS, presumed cardiac rupture, and chronic use of corticosteroids were excluded from the study. A total of 50 cases, 25 cases including patients who received clopidogrel (Group A) and 25 cases including patients who were either clopidogrel-naive or had not used clopidogrel within 5 days of undergoing surgery (Group B), were randomly selected from each site.

Major bleeding was defined as 1) >5 g/dL drop in hemoglobin, intracranial bleed, fatal bleed, or cardiac tamponade; 2) substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 4 units of blood (the CURE study definition); and 3) intracranial bleeding, hemorrhagic death, cardiac tamponade, or any clinically apparent bleeding associated with a decrease in hemoglobin of >5 g/dL or a >15% reduction in hematocrit-adjusted for red blood cell transfusions (the TIMI study definition).

Sample characteristics: A total of 596 patients (Group A, n=298; Group B, n=298) were included in the study. The mean age of the total study sample was 64 years, 68% were male and 89% were white. Patients in Group A were found to have a greater prevalence of prior cerebrovascular accident, MI, and PCI; these patients were also more frequently exposed to antifibrinolytic drugs in the operating room than were patients in Group B. Of the 596 patients included in the study, 577 case report forms included total cost information and 406 case report forms included both direct and overhead cost data for the pharmacoeconomic subanalysis.

Results: After analysis of the combined endpoint of major bleeding or reoperation, it was determined that exposure to clopidogrel 5 days or less prior to surgery was associated with a significantly elevated risk. The overall incidence of excessive or major bleeding, reoperation and LOS was found to be significantly influenced by clopidogrel exposure status. LOS was 1 day longer in Group A than in Group B. In addition, there was a significantly higher rate of reoperation in Group A than in Group B and the rate of major bleeding in Group A was significantly higher than in Group B (see the following table for primary and secondary endpoint results).

The risk of experiencing major bleeding was negatively related to the number of days between the last clopidogrel exposure and surgery reaching the background level of risk at 6 days prior to surgery. A significant relationship between older age and female gender on the risk of reoperation and major bleeding was found; however, even adjusting for these characteristics, exposure to clopidogrel still remained the most significant risk factor.

TABLE 5-18: Unadjusted Primary and Secondary Outcomes. Adapted from *J Am Coll Cardiol.* 2008;52:1693-1701.

Outcomes	Group A (n=298)	Group B (n=298)	p-value
Primary Outcomes			
Patients requiring reoperation, n (%)	19 (6.4)	5 (1.7)	0.004
Patients with excessive or major bleeding, n (%)[a]	71 (34.5)	53 (25.6)	0.049
Inpatient LOS, days (±SD)	9.7±6.0	8.6±4.7	0.016
Secondary Outcomes			
Reoperation for bleeding complication, n (%)	14 (4.7)	4 (1.3)	0.017
CURE major bleeding, n (%)	113 (53.8)	73 (34.9)	<0.001
TIMI major bleeding, n (%)	114 (54.3)	98 (46.9)	0.130
Non-life-threatening bleeding, n (%)[b]	56 (18.8)	55 (18.5)	0.916
In-hospital death, n (%)	4 (1.3)	1 (0.3)	0.373
Death/reinfarction/stroke, n (%)	8 (2.7)	5 (1.7)	0.400
Transfusion received, mean units (±SD)[c]	4.90 (±7.90)	2.03 (±3.75)	<0.001
Hospital readmission within 30 days	27 (9.1)	24 (8.1)	0.670
Postsurgical LOS, days (±SD)	7.2 (±5.53)	6.3 (±3.87)	0.054
ICU LOS, days (±SD)	2.7 (±3.17)	2.4 (±2.52)	0.059

CURE = Clopidogrel in Unstable angina to prevent Recurrent Events; ICU = intensive care unit; LOS = length of stay; SD = standard deviation; TIMI = Thrombolysis in Myocardial Infarction. [a] Some cases were missing the necessary Hg values for this definition; therefore, n = 206 for Group A and n = 207 for Group B. [b] Non-life threatening bleeding was bleeding that required treatment consisting of transfusion of ≥2 but <4 units of blood products in the combined intraoperative and postoperative periods. [c] Included were intraoperative and postoperative transfusions of all types of blood products (platelets, packed red blood cells, fresh frozen plasma, and cryoprecipitate).

Pharmacoeconomic subanalysis results—implications of clopidogrel exposure <5 days prior to surgery: In a substudy of the same data set, the inpatient costs and hospital charge data of the cohort were analyzed. Patients who had been exposed to clopidogrel within 5 days of their CABG procedure had significantly higher total costs than patients not exposed to the agent (p=0.004) (see the following table). Patients in Group A were also found to have a higher rate of reoperation (n=19 for Group A vs. n=5 for Group B) which was a primary driver of increased costs.

TABLE 5-19: Total Costs, Direct Costs, and Overhead Costs. Adapted from poster presented at: American Heart Association 9th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke; May 1-2, 2008; Baltimore, Maryland.

Costs **Median (range)**	**Group A**	**Group B**	**p-value**
Total costs	n=288 $28,602 ($9320-$136,101)	n=289 $25,442 ($8331-$131,806)	0.004
Direct costs	n=203 $18,969 ($6467-$97,067)	n=203 $17,831($4598-$93,309)	0.017
Overhead costs	n=203 $11,106 ($4453-$51,446)	n=203 $10,148 ($3733-$48,881)	0.006

Conclusion: The authors concluded that the exposure to clopidogrel within 5 days of CABG surgery resulted in poorer patient outcomes including higher rates of major bleeding and increased length of hospital stay. This exposure also resulted in avoidable increased health care costs.

Genetic Nonresponders to Clopidogrel and Associated Outcomes

Crespin DJ, Federspiel JJ, Biddle AK, et al. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis [Presentation]. Presented at: Personalized Medicine: Two Papers on The Cost Effectiveness of Genetic Tests for Determining Treatment for Patients With Acute Coronary Syndromes (ACS) Seminar; June 18, 2010: Chapel Hill, North Carolina.

Funding: National Institute on Aging, National Institute of General Medical Sciences, UNC-RTI Evidence Based Practice Center

Dates: Not applicable

Key findings:

- Utilizing a genotype driven clopidogrel administration strategy may not be the most cost-effective option.
- Universal use of ticagrelor increases QALYs for patients with ACS.

Study design: A decision tree/Markov model was developed to compare the cost effectiveness of genotype-driven administration of clopidogrel versus universal prescribing of ticagrelor in Medicare patients (66 years of age).

Endpoints: The endpoints assessed were life years and QALYs gained for each treatment strategy.

Methods: The decision tree/Markov model evaluated 2 treatment strategies.

- Patients receive CYP2C19*2 mutation testing and either receive ticagrelor (if mutation present) or clopidogrel (if mutation not present).
- Patients all treated with ticagrelor without genetic testing.

The Markov model assessed the movement of patients from different states after ACS, including MI, bleeding, dyspnea, and death.

Data regarding the risk of all-cause mortality and repeat MI were obtained from Medicare inpatient claims. Data comparing the clinical effectiveness of ticagrelor and clopidogrel were obtained from the PLATO trial; clopidogrel performance was adjusted, assuming a 30% nonresponder rate (from the CURE trial of clopidogrel vs placebo). Therapy was assumed to continue for 12 months post-ACS event. After 12 months, the HRs of ACS-related events were assumed to be equal in both treatment strategies. The cost of genotype testing, medical costs, and quality-of-life adjustments were obtained from the literature (see the following table).

TABLE 5-20: Model Inputs and Sources. Adapted from the presentation "Personalized Medicine: Two Papers on The Cost Effectiveness of Genetic Tests for Determining Treatment for Patients With Acute Coronary Syndromes (ACS). Seminar"; June 18, 2010: Chapel Hill, North Carolina.

Parameter	Input (USD 2009)
Cost of genotype test	$200
Cost of generic clopidogrel	$30/month[a]
Cost of ticagrelor	$164/month[b]
Medical cost of nonfatal MI/fatal MI	$18,390/$16,093
Medical cost of minor bleeding	$7491
Medical cost of monthly subsequent care ACS	$416

ACS = acute coronary syndrome; MI = myocardial infarction. [a] Cost of generic clopidogrel obtained from Red Book 2008. [b] Cost of ticagrelor was not known by the authors at the time of the study. The cost of ticagrelor was based on the initial cost of prasugrel.

Results: Cost-effectiveness results over a 1-, 5-, and 30-year period are shown in the table below. The majority of the cost difference between the 2 treatment strategies occurs in the first year: the incremental cost-effectiveness result (ICER) peaked at $111,835/QALY after 6 months of therapy. Over 30 years, the ICERs for universal prescribing of ticagrelor were $9161/QALY compared to the genotype-driven treatment.

TABLE 5-21: Base Case Model Results by Time Horizon. Adapted from the presentation "Personalized Medicine: Two Papers on The Cost Effectiveness of Genetic Tests for Determining Treatment for Patients With Acute Coronary Syndromes (ACS) Seminar"; June 18, 2010: Chapel Hill, North Carolina.

	Cost Per Patient	Outcome (QALY/patient)	Incremental Cost Per Patient	QALYs Gained	ICER Per QALY
After 1 year					
Genotype-driven	$6540	0.66	—	—	—
Universal ticagrelor	$7455	0.67	$915	0.01	$103,600
After 5 years					
Genotype-driven	$8533	2.89	—	—	—
Universal ticagrelor	$9595	2.95	$1062	0.06	$17,448
After 30 years					
Genotype-driven	$11,677	6.40	—	—	—
Universal ticagrelor	$12,953	6.54	$1276	0.14	$9161

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The ICER remained below $50,000/QALY until the monthly ticagrelor price was increased to $755 or a HR of 0.93 for death for ticagrelor relative to clopidogrel. Results of a probabilistic sensitivity analysis indicated that universal ticagrelor treatment strategy remained below $50,000/QALY in 97.4% of simulations. The cost-effectiveness acceptability curve indicated a 95% probability that universal ticagrelor is cost-effective compared with the genotype-driven strategy, given a maximum willingness to pay of $32,840.

Conclusion: Results of this economic model based on the PLATO clinical trial suggest that genotype-driven treatment with clopidogrel and ticagrelor may not be the most cost-effective option. Universal prescribing of ticagrelor was cost-effective, especially over a long-term time horizon.

5.1.2 EVIDENCE TABLE SPREADSHEETS

5.1.2.1 Spreadsheets for Published and Unpublished Clinical and Economic Studies for Labeled and Off-label Indications

TABLE 5-22: Summary Table of Other Clinical Studies for Labeled and Off-Label Indications of Ticagrelor (BRILINTA).

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
Phase III Studies					
PLATO PLATELET substudy Storey RF et al. *J Am Coll Cardiol.* 2010a;56:1456-1462. Online appendix. Available at: http://content.onlinejacc.org/cgi/content/full/j.jacc.2010.03.100/DC1.	Substudy of PLATO, a multicenter, double-blind, randomized study that compared TCG to CLP for prevention of major CV events in patients with ACS treated with ASA **Aim:** To assess the onset and extent of inhibition of platelet function in PLATO study patients	**LD Analysis** N = 24 CLP-naive patients at 1 center Treatment: • TCG 180-mg LD (n=12) or • CLP 300-mg LD (n=7) or • CLP 600-mg LD (n=5) All in the TCG group and 11 of 12 in the CLP group received ASA concomitantly. **MD Analysis** N = 69 patients at 2 centers, including those participants in the LD analysis Treatment: ≥28 days of • TCG 90 mg BID (n=37) or • CLP 75 mg QD (n=32) 35 (95%) of 37 TCG pts and 31 (97%) of 32 CLP pts received ASA concomitantly. • Percentages of pts in the treatment groups whose LTA responses were associated with an increase in risk of an ischemic event were determined by comparison with the previously established thresholds: a maximum LTA response to 20 μM	**Inclusion:** Same as those of the overall PLATO study **Exclusion:** Same as those of the overall PLATO study and the following: • Dipyridamole, cilostazol, or GP IIb/IIIa antagonist therapy within the prior 7 days • Ticlopidine therapy within the prior 14 days.	Inhibition of platelet function as measured by LTA, VerifyNow P2Y12 and VASP phosphorylation	**Results of LD Analysis** • More rapid and greater inhibition of platelet function during the first hours of treatment was observed with TCG LD than with either CLP LD. • One hour after dose administration, all but 1 patient treated with a TCG LD demonstrated greater inhibition of platelet function (ADP 20 μM, maximum and final extent) that was sustained until 12 h after dose administration. • Results of VN P2Y12 assays showed significantly greater inhibition with the TCG LD than with the CLP LD at 4 h after dose administration ($p<0.01$). In contrast, results of the VASP phosphorylation assays showed a nonsignificant trend toward greater inhibition by TCG at 4 h after dose administration. • When measures of inhibition of platelet function were evaluated in relation to thresholds of ischemic risk, there were few poor responders in the TCH group after LD administration; poor response was fairly common in patients given CLP LD. • Onset of IPA was more rapid for TCG LD than for CLP LD. • IPA at 1, 2, and 4 h after LD administration was significantly greater for the TCG group than for the CLP group. One hour after LD administration, IPA (maximum response to 20 μM ADP) was 54%±23% for the TCG group and 25%±17% for the CLP group ($p<0.01$). **Results of MD Analysis** • Maintenance therapy with TCG 90 mg BID achieved greater and more consistent inhibition of platelet function than did CLP 75 mg QD. • Similar patterns of platelet function inhibition were seen in comparisons of TCG and CLP groups in the UK with those in the US. • When measures of inhibition of platelet function after MD administration were evaluated in relation to thresholds of ischemic risk, few poor responders in the TCG group were found; poor response was fairly common in patients given CLP. • Inhibition of platelet function did not significantly differ between high-dose and low-dose ASA users within the TCG group (28±28 PRU vs. 32±33 PRU, respectively; p=NS) and within the CLP group (221±97 PRU vs. 192±96 PRU, respectively; p=NS) after

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
		ADP >50% and a final LTA response to 5 µM ADP >14%.			more than 28 days of maintenance therapy. • Platelet function responses in LTA and VN P2Y12 assays were greater for patients who received CLP and a PPI than for those who received CLP but no PPI. Platelet function responses did not differ between patients given TCG and a PPI and those given TCG but no PPI. • No additional safety results were presented.
Phase II Studies					
Effect of TCG vs. CLP on HPR during maintenance therapy Bliden et al. *Am Heart J*. 2011;162:160-165.	A planned subanalysis of pooled data from the ONSET/OFFSET and RESPOND studies. Platelet function was assessed using LTA, VerifyNow, and VASP phosphorylation. **Aim:** To compare the prevalence of HPR in patients randomized to ticagrelor and clopidogrel in the ONSET/OFFSET and RESPOND studies	N=209 patients TCG: n=106 CLP: n=103 **ONSET/OFFSET** Initial LD (Day 1): • TCG 180 mg x 1, or • CLP 600 mg x 1, or • Placebo Maintenance: TCG 90 mg or placebo in the evening on Day 1, followed by: • TCG 90 mg BID (n=57), or • CLP 75 mg QD (n=54), or • Placebo (n=12) for 6 weeks. All patients received ASA 75-100 mg QD. OFFSET period: Following the 6 week treatment phase, patients entered a 10-day drug-offset period during which they were given a final dose of the study drug on the first day of the offset period. **RESPOND** Patients randomized to: • TCG: 180 mg x 1, then 90 mg BID, or	**Inclusion:** Enrollment in the ONSET/OFFSET trial or the RESPOND trial	Published cutoff points associated with post–PCI ischemic risk were used to define HPR: • LTA: >59%platelet aggregation induced by 20 µM ADP • VN assay: >235 PRU • VASP assay: 50% PRI	• TCG was associated with a significantly lower prevalence of HPR versus CLP at 2, 4, 8, and 24 hours, and ≥2 weeks post-dose ($p<0.0001$ for all post-dose comparisons as measured by all assays). • Thirty minutes after the LD, prevalence of HPR (based on LTA) was 33% with TCG and 83% with CLP. After 1 hour, 97% of TCG-treated patients were below HPR predefined cutoff points of HPR, whereas 44% of CLP-treated patients demonstrated HPR up to 4 hours after the LD. • During the maintenance phase, the prevalence of HPR remained high in CLP group (21%) and lower in the TCG group (2%). • HRP at 24 hours after the last maintenance dose was greater in CLP-treated patients (LTA: 21% vs. 2%; VerifyNow: 35% vs. 0%; VASP phosphorylation: 65% vs. 5%; $p<0.001$ for all comparisons) compared to TCG-treated patients. • The prevalence of HPR was similar between TCG- and CLP-treated patients at 48 hours after the last maintenance dose; however, it was higher at 72 hours and 120 hours with TCG compared to CLP as measured by LTA (60% vs. 45% and 80% vs. 66%, respectively; $p<0.05$ for both comparisons).

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
		• CLP: 600 mg x 1, then 75 mg QD for 14±2 days All CLP nonresponders crossed over to the other treatment for an additional 14±2 days. Half of CLP responders continued with the same treatment while the other half switched to the other treatment for 14±2 days. Patients who switched treatments received a LD followed by the maintenance dose.			

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results

Recovery time of platelet function in ONSET/OFFSET
 	
Storey et al. Presented at: European Society of Cardiology Congress; August 28-September 1, 2010; Stockholm, Sweden. *Eur Heart J.* 2010f;31(abs suppl):389. Abs P2313.
	Subanalysis of ONSET/OFFSET study, a Phase II multicenter, randomized, double-blind, double-dummy, parallel-group study to determine the onset and offset of the antiplatelet effect of TCG compared to high-LD CLP and PBO in patients with stable CAD.
	
	Aim: To evaluate time to recovery of platelet function after D/C of TCG and CLP in patients with a high response on treatment
		N=123 in ONSET/OFFSET
		
		• **Initial LD (Day 1):**
		  ○ TCG 180 mg x 1, or
		  ○ CLP 600 mg x 1, or
		  ○ PBO
		• **Maintenance:** TCG 90 mg or PBO in the evening on Day 1, followed by:
		  ○ TCG 90 mg BID (n=57), or
		  ○ CLP 75 mg QD (n=54), or
		  ○ PBO (n=12) for 6 weeks.
		• All patients received ASA 75-100 mg QD.
		• **OFFSET period:** Following the 6 week treatment phase, patients entered a 10-day drug-offset period during which they were given a final dose of the study drug on the first day of the offset period.
			Inclusion:
			• Age ≥18 years
			• Stable CAD
			• ASA 75-100 mg/day
			
			Exclusion:
			• History of ACS in prior 12 months
			• Any indication for antithrombotic therapy
			• CHF
			• LVEF <35%
			• FEV_1 or FVC below LLN
			• Bleeding diathesis
			• Severe pulmonary disease
			• Pregnancy
			• Smoker
			• Treatment with moderate or strong P450 3A inhibitors, substrates or strong P450 3A inducers
			• Platelets <100,000/mm^3
			• Hb <10 g/dL
			• HbA_{1c} ≥10%
			• History of drug addiction or alcohol abuse in past 2 years
			• NSAID use
			• CrCL <30 mL/min
				Primary:
				• ONSET: IPA (20 µmol/L ADP, final extent) 2 h after the first dose
				• OFFSET: Slope of IPA between 4 and 72 h after the last dose
					• A high response was defined as IPA >75% (ADP 20 µM, final extent) at 4 h postdose, <120 PRU at 8 h postdose, and PRI <50% at 8 h postdose.
					• Thirty-nine patients in the TCG group and 17 patients in the CLP group had IPA >75% at 4 h postdose. The rate of platelet recovery was faster with TCG between 4 and 48 h vs. CLP; mean IPA was significantly lower with TCG at all time points between 48 and 168 h vs. CLP.
					• The rate of offset of antiplatelet activity, estimated by the slope of the IPA curve between 4 and 72 hrs postdose, was greater with TCG vs. CLP (–1.11 vs. –0.67 IPA %/h, p<0.0001).
					• Similar patterns of recovery of platelet function were noted with the VN $P2Y_{12}$ assay and VASP phosphorylation assay.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
ONSET/OFFSET and RESPOND Genotype Studies Tantry et al. *Circ Cardiovasc Genet.* 2010; 3:556-566	Substudy of 2 Phase II, multicenter, randomized, double-blind, double-dummy studies, the ONSET/OFFSET study and the RESPOND study **Aim:** To determine the effect of genotypically predicted CYP2C19 metabolizer status on platelet reactivity of ticagrelor versus clopidogrel from the ONSET/OFFSET and RESPOND studies and to compare the platelet reactivity of treatments within specific genotypes	N=174 patients who underwent genotyping in the ONSET/OFFSET and RESPOND studies. • TCG 180 mg x 1, then 90 mg BID (n=92) • CLP 600 mg x 1, then 75 mg QD (n=82) Refer to ONSET/OFFSET and RESPOND study summaries above for further details.	**Inclusion**: patients age ≥18 years with stable CAD receiving ASA (75-100 mg daily) therapy **Exclusion:** ACS within 12 months of screening, history of bleeding diatheses, severe pulmonary disease, pregnancy, concomitant therapy with moderate CYP3A inhibitors or strong inducers, atrial fibrillation, mitral stenosis, prosthetic heart valve requiring antithrombotic treatment, platelet count $< 100{,}000/mm^3$ or hemoglobin < 10g/dL Refer to ONSET/OFFSET and RESPOND study summaries above for further details.	Platelet function with TCG vs. CLP in the following genotype groups: • CYP2C19 LOF alleles *2, *3, *4, *5, *6, *7, *8 • CYP2C19 GOF allele *17 • ABCB1 Platelet function data were categorized based on metabolizer status (Group I), LOF (Group II) and GOF carrier status (Group III), and ABCB1 genotype.	• In patients treated with ASA alone, there was no significant influence of genotypes on platelet function. • ABCB1 genotype did not influence platelet function before or during therapy with ticagrelor or CLP. • Patients treated with ticagrelor had significantly ($p \leq 0.0016$) lower platelet function as measured by all assays than patients treated with CLP among all 2C19 genotypes studied with the exception of poor metabolizers due to small patient numbers (n=5) having wide confidence intervals in the data • Within treatment groups, there was no influence of genotype on platelet function in the ticagrelor group either postloading or during maintenance treatment. • In the clopidogrel group, the influence of genotype on platelet function as measured by Verify Now $P2Y_{12}$ was noted postloading (p=0.019 among different metabolizers; p=0.01 between LOF carriers and LOF noncarriers; p=0.28 among GOF, LOF, and extensive metabolizers). • The influence of genotype was more evident during maintenance therapy with clopidogrel as measured by VerifyNow $P2Y_{12}$ assay (p=0.006 among different metabolizers; p=0.002 between LOF carriers and LOF noncarriers; p=0.007 among GOF, LOF, and extensive metabolizers). • During maintenance therapy, ticagrelor was associated with significant lower platelet function as measured by all assays in *1/*1, *1/*2, *1/*17, and *2/*17 diplotypes ($p \leq 0.009$). • In clopidogrel-treated patients, there was a significant influence of diplotype status on platelet function as measured by VerifyNow $P2Y_{12}$ assay and a trend towards 20 µM/L ADP-induced aggregation and VASP phosphorylation ($p \leq 0.006$). • No safety data was reported.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results

Effect on inflammatory biomarkers
 	
Husted et al. *Clin Cardiol*. 2010;33:206-212.
	• Analysis of the DISPERSE-2 trial, a Phase II randomized, double-blind, double-dummy, multicenter trial
	• The inflammatory markers—CRP, sCD40L, MPO, and IL-6—were analyzed at baseline (Day 1, randomization, predose), prior to hospital discharge (Days 2-4), and 4 weeks.
	
	Aim: To compare TCG+ASA with CLP+ASA for effects on the inflammatory biomarkers CRP, sCD40L, MPO, and IL-6
		N=990
		
		• Treatment with one of the following lasted up to 12 weeks:
		  ○ TCG 90 mg BID (half of the patients received a 270-mg LD); n=334
		  ○ TCG 180 mg BID (half of the patients received a 270-mg LD); n=323
		  ○ CLP (CLP-naive: 300-mg LD, then 75 mg QD; CLP-pretreated: 75 mg QD); n=327
		• Standard medical and interventional treatment for ACS, including ASA (initial dose up to 325 mg, subsequent doses of 75-100 mg QD)±GP IIb/IIIa inhibitor
			Inclusion criteria reported by Husted et al (2010) were the following:
			
			• Hospitalization for NSTE-ACS in the past 48 hrs
			• Ischemic symptoms at rest ≥10 min
			• Biochemical marker evidence of MI or ECG evidence of ischemia.
			
			Exclusion criteria were not reported by Husted et al (2010).
				The inflammatory markers (CRP, sCD40L, MPO, and IL-6) over various time points	• No significant differences between treatment groups were found for any of the inflammatory markers studied at any of the time points measured (baseline, hospital discharge, and 4 weeks).
					• CRP levels were elevated from baseline to discharge and decreased from baseline to 4 weeks in all groups.
					• IL-6 levels were unchanged from baseline to discharge and decreased from baseline to 4 weeks in all groups.
					• MPO levels showed little change from baseline and were slightly lower at discharge and 4 weeks.
					• sCD40L levels showed little change from baseline and were slightly lower at discharge but similar to baseline at 4 weeks.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
PK and PD of TCG in patients with stable CAD Husted et al. *Circulation.* 2009;120:S1102. Abs 5494.	TCG PK was evaluated in patients with stable CAD treated with ASA in 2 studies: • ONSET/OFFSET, a multicenter, randomized, double-blind, parallel-group study • RESPOND, a 2-way crossover study	**ONSET/OFFSET** • Initial LD (Day 1): o TCG 180 mg x 1, or o CLP 600 mg x 1, or o PBO • Maintenance: TCG 90 mg or PBO in the evening on Day 1, followed by: o TCG 90 mg BID (n=57), or o CLP 75 mg QD (n=54), or o PBO (n=12) for 6 weeks. • All patients received ASA 75-100 mg QD. **RESPOND** Patients received 75-100 mg ASA daily. CLP nonresponders (n=41) and CLP responders (n=57) were randomized to 14 days of CLP 75 mg QD following a 600-mg LD or TCG 90 mg BID following a 180-mg LD, with no washout between treatments.	Not specified in the meeting abstract	PK parameters	**ONSET-OFFSET** • C_{max}, t_{max}, and $t_{1/2}$ values of TCG 90 mg BID were 733 ng/mL, 2 hours, and 10.2 hours for TCG, respectively, and 210.3 ng/mL, 2.1 hours, and 12.8 hours for AR-C124910XX, respectively. These values were comparable to those seen previously in healthy subjects. • Trough plasma level of TCG was 304.6 ng/mL, and trough plasma level of AR-C124910XX was 120.7 ng/mL. **RESPOND** • Mean C_{max} and area under the curve from 0 to infinity ($AUC_{0-\infty}$) of TCG following 2 weeks of maintenance doses of 90 mg BID were similar between CLP responders treated with 75 mg QD (724.2 ng/mL and 3982.7 ng·h/mL, respectively) and CLP nonresponders treated with 75 mg QD (764.4 ng/mL and 3985.2 ng·h/mL, respectively). • PK of TCG was not affected when TCG was administered 24 hours post-CLP dosing. • No safety results were reported in the abstract.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results

PK and PD of TCG in patients with NSTE-ACS
 	
Storey et al. *J Am Coll Cardiol.* 2007;50:1852-1856.
	Substudy of the DISPERSE-2 trial, a Phase II randomized, double-blind, double-dummy trial
	Aim: To assess the PD and PK of TCG vs. CLP in patients with NSTE-ACS treated with ASA
		• 91 with NSTE-ACS enrolled
		• 89 received study medication and had evaluable data.
		
		Treatment:
		
		• Treatment for up to 12 weeks with either:
		  ○ TCG 90 mg BID (half received 270-mg LD)
		  ○ TCG 180 mg BID (half received 270-mg LD)
		  ○ CLP (CLP-naive: 300 mg LD, then 75 mg QD; CLP-pretreated: 75 mg QD)
		• Standard medical and interventional treatment for ACS, including ASA at an initial dose of up to 325 mg followed by 75-100 mg QD, with or without GP IIb/IIIa inhibitor.
			Inclusion:
			• Ages 18 years or older
			• Hospital admission hospital within prior 48 hours for ischemic chest pain associated with ischemic ECG changes (no sustained ST-segment elevation) and/or abnormally increased cardiac markers
			Exclusion:
			• PCI within the prior 48 hours
			• Increased bleeding risk
			• Thrombolytic therapy within the prior 7 days
			• Treatment with strong CYP3A4 inhibitors or substrates with narrow therapeutic index
			• Treatment with GP IIb/IIa inhibitors within prior 24 hours or 7 days (abciximab), UFH within 24 hours, or dipyridamole within 24 hours of randomization
				ADP-induced platelet aggregation, PK	**PK Results:**
					CLP-naive
					• Mean levels of TCG in CLP-naive patients were highest at the 2-hour time point; mean levels of AR-C124910XX peaked at 2 to 4 hours with levels 2- to 5-fold lower vs. TCG levels.
					
					CLP-pretreated:
					• Levels of TCG and AR-C124910XX were similar in the CLP-pretreated patients, indicating that the PK of TCG is not affected by CLP pretreatment.
					
					PD Results:
					CLP-naive
					• Ticagrelor inhibited platelet aggregation dose-dependently. IPA levels for all ticagrelor doses were greater than the maximum level of inhibition seen after the clopidogrel LD; it took 4 hours to achieve the maximum IPA ($p<0.001$ for all ticagrelor groups vs. clopidogrel at 4 hours, final aggregation response).
					• IPA by ticagrelor remained stable at 4 weeks, with the most consistent response being seen with ticagrelor 180 mg twice daily.
					
					CLP-pretreated:
					• Both doses of ticagrelor inhibited platelet function in a dose-dependent manner, irrespective of previous treatment with clopidogrel.

Study/Citation	Study Design	Treatment/N	Inclusion/Exclusion Criteria	Endpoints	Results
PD, PK, and safety of TCG in patients with atherosclerosis Husted S et al. *Eur Heart J.* 2006;27:1038-1047.	Randomized, double-blind, double-dummy, multinational study **Aim:** To assess the PD, PK, and safety of TCG with ASA relative to CLP with ASA in patients with atherosclerosis	N=200 **Treatment:** • TCG 50 mg BID (n=41), • TCG 100 mg BID (n=39), • TCG 200 mg BID (n=37), • TCG 400 mg QD (n=46), or • CLP 75 mg QD (n=37) Treatment lasted 28 days, and all received ASA 75-100 mg QD.	**Key Inclusion Criterion:** ASA (75-100 mg QD) for confirmed atherosclerotic disease for ≥2 wks before randomization **Key Exclusion Criteria:** • Recent ACS • PCI with ballon or stent • Conditions with increased risk of bleeding • SCr ≥1.2× ULN • Hb ≥5% below LLN	**Main PD Measure:** inhibition of ADP-induced platelet aggregation **Main Safety Measure:** incidence of AEs	**PK Results:** • Plasma concentrations of TCG and AR-C124910XX were stable and predictable at steady state. • Plasma concentrations of TCG and AR-C124910XX increased linearly and in proportion to the dose administered on Day 1. At Day 28, relative to the 50 mg and 100 mg BID doses, slightly greater than dose-proportional PK and correspondingly lower total plasma oral clearance (CL/F) were observed with TCG 200 mg BID and TCG 400 mg QD. • At steady state, AR-C124910XX exposure was approximately 35% of that of TCG. • C_{max} and AUC for TCG and AR-C124910XX did not vary significantly with age or gender. **Safety Results:** • The most common AE was bleeding, which increased in incidence with higher TCG doses (vs. TCG 50 mg BID or CLP). GI hemorrhage with decreased Hb was reported in a patient receiving TCG 400 mg QD. • Other commonly reported AEs were dyspnea, dizziness, and headache. The incidence of dyspnea appeared to increase with increasing dose of TCG. No reports of dyspnea were considered serious. • Uric acid levels increased by 5%-10% in all TCG groups and decreased by approximately 10% in the CLP group. • No deaths were reported.

ACS = acute coronary syndrome; ADP = adenosine diphosphate; AE = adverse event; ASA = aspirin; $AUC_{0-\infty}$ = area under the plasma-time concentration curve from time 0 to infinity; AUC_{0-8} = area under the plasma concentration-time curve over 8 hours; $AUC_{0,t}$ = area under the plasma concentration-time curve within the dosing interval; CAD = coronary artery disease; CHF = congestive heart failure; CL/F = plasma oral clearance; C_{max} = peak plasma concentration; CLP = clopidogrel; CrCL = creatinine clearance; CRP = C-reactive protein; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GP = glycoprotein; GOF = gain of function; Hb = hemoglobin; IL-6 = interleukin-6; IPA = inhibition of platelet aggregation; LD = loading dose; LLN = lower limit of normal; LOF = loss of function; LTA = light transmittance aggregometry; LVEF = left ventricular ejection fraction; MD = maintenance dose; MPO = myeloperoxidase; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; NSTE = non-ST-elevation; PBO = placebo; PCI = percutaneous coronary intervention; PD = pharmacodynamics; PLATO = PLATelet inhibition and patient Outcomes; PK = pharmacokinetics; PPI = proton pump inhibitor; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction units; pts = patients; sCD40L = soluble CD40 ligand; SCr = serum creatinine; $t_{½}$ = terminal-phase elimination half-life; TCG = ticagrelor; UFH = unfractionated heparin; ULN = upper limit of normal; UK = United Kingdom; VASP = vasodilator-stimulated phosphoprotein; VN = VerifyNow.

TABLE 5-23: Summary Table for Published and Unpublished Economic Studies for Labeled and Off-label Indications.

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Costs and Health Outcomes Based on the Study of PLATelet Inhibition and Patient Outcomes (PLATO)			
In House Data. Study of Platelet Inhibition and Patient Outcomes (PLATO) Health Economics (HECON) Substudy. AstraZeneca LP, 2011.	**Design:** Health Economic substudy of the PLATO study **Sample Size:** 18,624 patients (clopidogrel, n=9291; ticagrelor, n=9333) Eligible for 12-month follow-up: 10,686 (clopidogrel, n=5339; ticagrelor, n=5347) Low-dose ASA cohort: 15,439 (clopidogrel, n=7706; ticagrelor, n=7733) Low-dose ASA cohort eligible for 12-month follow-up: 8941 (clopidogrel, n=4460; ticagrelor, n=4481) **Treatments:** ticagrelor clopidogrel	**Inclusion:** All patients from all sites of the PLATO trial Low-dose ASA cohort included patients who were on a daily maintenance ASA dose of ≤100 mg per day **Exclusion:** Same exclusion criteria as overall PLATO trial Note: All medication utilization and costs were excluded from analysis.	**Endpoints** **Reduction in resource use with ticagrelor** • All-cause inpatient bed days: 0.21/patient • PCI: 0.01/patient • CABG: 0.01/patient **Medical care costs for patient eligible for 12-month follow-up** • Total Costs: clopidogrel: $35,152; ticagrelor: $34,133 • Difference (95% CI): $1019 (-101, 2138); p=0.075 • Reduction in total medical care costs driven by fewer all-cause inpatient bed days ($787 [95% CI: -200, 1774]; p=0.118) and CV interventions (difference: $202 [95% CI: -42, 446]; p=0.105) **Medical care costs for all PLATO patients** • Total Costs: clopidogrel: $34,001; ticagrelor: $33,187 • Difference (95% CI): $815 (-4 1633); p=0.051 • Reduction in total medical care costs driven by fewer all-cause inpatient bed days ($526 [95% CI: -193, 1245]; p=0.15) and CV interventions ($254 [95% CI: 68, 440]; p=0.007) ***Low-dose ASA subgroup*** **Reduction in resource use with ticagrelor—low-dose ASA cohort** • All-cause inpatient bed days: -0.33/patient • CABG: -0.01/patient **Medical care costs for patient eligible for 12-month follow-up— low-dose ASA cohort** • Total Costs: clopidogrel: $35,598; ticagrelor: $34,455 • Difference (95% CI): $1143 (-84, 2,369); p=0.068 • Reduction in total medical care costs driven by fewer all-cause inpatient bed days ($909 [95% CI: -176, 1995]; p=0.101) and CV interventions ($231[95% CI: -20, 482]; p=0.072) **Medical care costs for all low-dose ASA cohort** • Total Costs: clopidogrel: $34,415; ticagrelor: $33,414 • Difference (95% CI): $1002 (108, 1895); p=0.028 • Reduction in total medical care costs driven by fewer all-cause inpatient bed days ($741 [95% CI: -45, 1,528]; p=0.06) and CV interventions ($243 [95% CI: 47, 439]; p=0.015)

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Economic Burden of ACS in a Managed Care Setting			
Etemad and McCollam. *J Manag Care Pharm*.2005; 11: 300-306.	**Design:** Descriptive, retrospective, analysis of claims data from a large MCO with >3 million members **Sample Size:** 13,731 patients **Index diagnosis:** UA (51.7%), acute MI (48.3%) **Treatments:** N/A	**Inclusion:** Patients age ≥18 years with new onset UA or acute MI with at least 6 months of eligibility prior to event **Exclusion:** Previous diagnosis of ACS	**Endpoints** Rate of Hospitalization: • 93% of patients had at least 1 hospitalization during the study period; mean number of hospital days per patient-month was 0.65. • Total of 3641 patients (26.5%) had more than 1 hospitalization. • There were 6770 hospitalizations after the index date. Rate of Revascularization: • Revascularization procedures were completed in 51% of patients with the majority receiving the procedure on their index event date (69%). • Stents were the majority of procedures completed (34%), followed by CABG (14%) and PTCA (2%). Health Care Costs: • Total health care costs: $309 million ($22,529 per patient or $2312 per patient-month) • Hospitalization costs: $221 million • Office/Outpatient costs: $37 million • Pharmacy costs: $23 million • ER visits: $12 million Health Care Utilization: • Revascularization procedures: 6929 patients (50.5%) • CABG: 1927 (14%) • PTCA: 323 (2.4%) • Stent: 4679 (34.1%) Medication Use in Follow-up: • Cholesterol-lowering medication—statin: 55.9% • Cholesterol-lowering medication—nonstatin: 10.3% • Beta-blocker: 58.4% • ACE inhibitor: 37.6% • Angiotensin-2 blocker: 6.9% • Calcium channel blocker: 24.2%

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Berenson et al. *Curr Med Res Opin*. 2010; 26:329-336.	**Design:** 2 retrospective observational studies, PharMetrics and HFHS **Sample Size:** 108,443 patients (HFHS hospitals: n=11,266; PharMetrics n=97,177) **Treatments:** N/A	**Inclusion:** Diagnosis of UA or MI or an ACS-related procedure as identified by ICD-9 procedure or diagnosis code or CPT code for MI, UA, CABG, stent placement, or PCI **Exclusion:** Patients aged <18 years or enrolled in the health plan for less than 6 months prior to the index date	**Endpoints** Direct Charges Related to ACS Rehospitalization: • Mean charges for all ages and over or under age 65 were similar for both databases for ACS-related rehospitalization. • Both databases showed extra mean charges of approximately $52,000 for rehospitalizations. Predictors of Increased ACS Charges: *HFHS:* Increase in charges was caused by CABG ($56,385), PCI ($16,844), and stent ($8199) all at rehospitalization, and LOS ($6759). All were significant. *PharMetrics:* Increase in charges was caused by CABG ($74,642), stent ($31,363), PCI ($22,379), acute MI ($6511) all at rehospitalization, and LOS ($4223). All were significant. Predictors of Increased LOS: • *HFHS:* Increase in LOS was caused primarily by CABG at rehospitalization (5.5 days) and at index (1.4 days), by acute MI at rehospitalization (2.6 days), increased age (1.1 days) and history of comorbidities (≤1 day). • *PharMetrics:* Increase in LOS was caused primarily by CABG at rehospitalization (4.9 days) and at index (1.0 days), by acute MI at rehospitalization (1.7 days), history of renal disease (2.1 days)and other comorbidities (≤1.5 days).

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Menzin et al. *Curr Med Res Opin*. 2008;24:461-468.	**Design:** Retrospective single-cohort study using administrative claims data of patients enrolled in employer-sponsored health plans **Sample Size:** 16,321 patients enrolled in employer-sponsored health plans **Treatments:** N/A	**Inclusion:** Hospitalization between January 2001 and December 2002 with a diagnosis of ACS (ICD-9-CM codes = 410.xx or 411.1); ≥35 years; ≥12 months of continuous coverage prior to the index admission **Exclusion:** Hospitalization or medical claim related to ACS in the 12 months prior to the index admission	**Endpoints** Characteristics of Initial Hospitalization: • Mean LOS: 4.6±6.7 days • Mean cost: $22,921±31,400 • Revascularization procedure: 46.3% of patients IHD-related Rehospitalization Rate: • 21.1% of patients were readmitted within 1 year of initial hospitalization. • 1 rehospitalization: 16.1% • 2 rehospitalizations: 3.5% • ≥3 rehospitalizations: 1.6% Characteristics of IHD-related Rehospitalization: • Mean time to rehospitalization: 58.1±78.5 days from initial hospitalization discharge • Mean cost: $28,637±32,972 • Revascularization procedure: 53% Predictors of Rehospitalization: The strongest predictors of rehospitalization were found to be comorbidities (HR 1.53; 95% CI: 1.37, 1.71), ACS listed as primary diagnosis at initial hospitalization (HR 1.50; 95% CI: 1.40, 1.61) , age >55 years (HR 1.24; 95% CI: 1.07, 1.44). Costs in the First Year Following Initial Hospitalization: ACS-related costs: $26,931 *Distribution by cost category:* • Inpatient: 11.9% • Outpatient:1.9% • Pharmacy: 1.2% • Initial Hospitalization: 85.1%

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Chastek et al. *Curr Med Res Opin*. 2009;25:2845-2852.	**Design:** Retrospective, administrative claims-based data analysis from a large US managed care plan **Sample size:** 9135 patients (cost analysis) (2241 rehospitalized once; 565 rehospitalized twice or more) **Treatment:** Implantation of a stent followed by use of clopidogrel	**Inclusion:** Patients aged ≥18 years enrolled in a commercially insured health plan, hospitalized for ACS between January 2000 and December 2004, had a stent implanted during the index hospitalization, had at least 1 prescription for clopidogrel within 7 days of discharge following the index hospitalization, and continuously enrolled in the plan for 12 months following the index hospitalization **Exclusion:** Patients who had a prescription for either an antiplatelet or anticoagulation drug prior to their index hospitalization, or filled a prescription for any other antiplatelet drug during the follow-up period	**Endpoints** Total Cost of Care Between Patients Readmitted Following the Initial Hospitalization vs Those Not Readmitted: For those patients who experienced a second hospitalization, the mean total costs were $22,852 higher than those patients who were not hospitalized (p<0.001). Total Costs Associated With a Second Ischemic Event-related Hospitalization to Costs Associated With the Index Hospitalization: • Total cost of the second hospitalization was slightly lower than the initial hospitalization: $20,601 for the first hospitalization vs. $19,489 for the second hospitalization (p=0.03). • Mean costs in the 18 months following the second hospitalization were almost twice as high as the mean costs in the 18 months following the index hospitalization. • Results indicate that preventing a second hospitalization not only prevents the costs of the hospitalization itself, but also prevents the higher subsequent care costs seen following the second event.

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Rehospitalization Rates, Mortality Rates, and Hospital Costs			
Tunceli et al. Poster presented at: International Society Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 21-25, Baltimore, Maryland.	**Design:** Retrospective, observational medical claims cohort study using administrative medical claims data from the HealthCore Integrated Research Database **Sample Size:** 30-day analysis: 59,947 patients • STEMI, n=13,085 • NSTEMI, n=17,810 • Acute MI NOS, n=5601 • UA, n=23,451 365-day analysis: 34,597 patients • STEMI, n=7620 • NSTEMI, n=9222 • Acute MI NOS, n=3022 • UA, n=14,733 **Treatments:** N/A	**Inclusion:** Patients aged ≥18 years with ≥1 medical claim for an inpatient hospitalization for ACS between January 2007 and May 2010, and ≥1 claim for ACS-related procedure or another diagnosis; continuously enrolled for 12 months prior to the start of the initial ACS hospitalization event All MI patients were also required to have ≥1 day of inpatient stay or discharge status determined as death. **Exclusion:** Patients with ACS events within 1 year prior to initial hospitalization	**Endpoints** **30-day all-cause rehospitalization rate** All ACS patients: 16.3% STEMI: 16.4% NSTEMI: 19.0% Acute MI NOS: 20.6% UA: 13.3% **30-day ACS-related rehospitalization rate** All ACS patients: 6.3% STEMI: 8.8% NSTEMI: 6.6% Acute MI NOS: 4.5% UA: 5.2% **12-month all-cause rehospitalization rate** All ACS patients: 41.3% STEMI: 39.0% NSTEMI: 46.4% Acute MI NOS: 46.6% UA: 38.2% **12-month ACS-related rehospitalization rate** All ACS patients: 16.6% STEMI: 20.5% NSTEMI: 17.6% Acute MI NOS: 14.6% UA: 13.3% **30-day mortality rate (n=59,947)** All ACS patients: 2.4% STEMI: 1.8% NSTEMI: 4.3% Acute MI NOS: 5.2% UA: 0.5% **12-month mortality rate (n=34,547)** All ACS patients: 7.0% STEMI: 5.1% NSTEMI: 11.6% Acute MI NOS: 12.9% UA: 2.6%

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Hess et al. Poster presented at: The American Heart Association's Quality of Care and Outcomes Research Cardiovascular Disease and Stroke 2011 Scientific Conference, May 12-14, 2011, Washington, DC.	**Design:** Retrospective, claims-based cohort study of patients with newly diagnosed ACS rehospitalization using hospital charge detail, practitioner, and prescription claims data and consumer insights (mortality) databases **Sample Size:** All patients: 17,904 patients • STEMI, n=2383 • NSTEMI, n=8585 • UA, n=5775 • Acute MI other, n=1161 Patients aged ≥65 years: 12,627 • STEMI, n=1518 • NSTEMI, n=6524 • UA, n=3705 • Acute MI other, n=880 **Treatments:** N/A	**Inclusion:** Patients aged ≥18 years with a new case of ACS diagnosed during inpatient hospitalization during the study period; ≥1 year of medical or hospital claims data pre-index and either ≥1 year post-index or with a recorded mortality post-index; ≥6 months of pharmacy claims data pre-index and either ≥1 year post-index or with a recorded mortality post-index **Exclusion:** Patients missing age or gender data and those with a continuing episode of ACS at time of index hospitalization	**Endpoints** **30-day all-cause rehospitalization rate / subset of patients ≥65 years** All ACS patients: 14.7% / 15.1% STEMI: 12.7% / 13.2% NSTEMI: 17.1% / 17.6% UA: 12.6% / 12.6% Acute MI NOS: 10.8% / 10.8% **30-day ACS-related rehospitalization rate / subset of patients ≥65 years** All ACS patients: 5.5% / 5.8% STEMI: 7.6% / 7.6% NSTEMI: 7.0% / 7.3% UA: 2.8% / 2.8% Acute MI NOS: 3.9% / 4.1% **30-day all-cause rehospitalization charges for all ACS patients / subset of patients ≥65 years** All: $13,160 / $13,353 STEMI: $12,334 / $12,153 NSTEMI: $16,338 / $16,410 UA: $9602 $9344 Acute MI NOS: $9051 / $9642 **30-day ACS-related rehospitalization charges for all ACS patients / subset of patients ≥65 years** All: $7216 / $7243 STEMI: $8582 / $7918 NSTEMI: $9271 / $9408 UA: $3984 / $3425 Acute MI NOS: $5283 / $6101 **12-month all-cause rehospitalization rate / subset of patients ≥65 years** All ACS patients: 37.7% / 38.1% STEMI: 31.3% / 32.5% NSTEMI: 39.9% / 40.1% UA: 39.7% / 39.9% Acute MI NOS: 25.4% / 25.1% **12-month ACS-related re-hospitalization rate / subset of patients ≥65 years** All ACS patients: 12.5% / 12.5% STEMI: 12.7% / 12.5% NSTEMI: 14.3% / 14.5% UA: 10.9% / 10.3% Acute MI NOS: 7.0% / 6.6% **12-month all-cause rehospitalization charges for all patients / subset of patients ≥65 years** All ACS patients: $53,052 / $51,560 STEMI: $38,479 / $36,246 NSTEMI: $60,658 / $58,003 UA: $51,626 / $50,302 Acute MI NOS: $33,810 / $35,510

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
			12-month ACS-related rehospitalization charges for all patients / subset of patients ≥65 years All ACS patients: $19,838 / $19,160 STEMI: $17,306 / $14,950 NSTEMI: $23,269 / $22,901 UA: $17,566 / $16,000 Acute MI NOS: $10,969 / $11,995
Access to Therapy in ACS			
Philipson et al. *Am J Manag Care.* 2010; 16:290-297.	**Design:** Retrospective, longitudinal outcomes study using administrative claims data of patients enrolled at health plans offered by 26 large private employers **Sample Size:** 14,325 privately insured ACS patients **Treatments:** • Antiplatelet drugs were filled 6.9 times per patient on average during Year 1 following stent placement • Antiplatelet drugs were filled 9.2 times per patient during Year 2	**Inclusion:** Patients with new onset ACS and at least 1 stent placement **Exclusion:** Previous hospitalization for ACS and prior antiplatelet use in the 12 months preceding stent placement	**Endpoints** Adoption of Antiplatelet Therapy Over the 40 Days After Implantation of the Index Stent: • Patients with ACS who had higher coinsurance were less likely to adopt outpatient antiplatelet therapy within the first month after stent implantation (p<0.01). • At 40 days after stent implantation, 90% for low cost-sharing compared with 86% for high cost-sharing had adopted therapy (p<0.01). Probability of Discontinuing Antiplatelet Therapy: • From 3 to 12 months after stent implantation, there was approximately a 1.8% greater chance of discontinuing therapy in the high cost-share group (p<0.01). • Patients with ACS who had higher coinsurance were more likely to discontinue treatment in the first year after stent implantation (p<0.01). Number of ACS Hospitalizations per Patient: 0.47 hospitalizations per patient in the high cost-share group compared to 0.4 in the low cost-sharing group (p<0.01). Annual Expenditures for ACS Rehospitalizations Between the Low and High Cost-sharing Plans: • First-year expenditures on ACS hospitalizations increased in the high cost-sharing group by $2796 compared to the low cost-sharing plan, which was shared by the patient and the insurance plan. • Taking into account the insurance company saved $1577 in pharmaceutical costs by passing those costs to the patients, the high cost-sharing plan still lost $603 per patient due to the higher hospitalization costs. *ACS Hospitalization Expenditures—First Year:* • Low cost-sharing plans: $7361 • High cost-sharing plans: $10,157 • Difference: 38%; p<0.01 *ACS Hospitalization Expenditures—Second Year:* • Low cost-sharing plans: $5146 • High cost-sharing plans: $,904 • Difference: -4.7%; p=0.82

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Hess et al. Adherence to medications with once-a day (QD) and twice-a-day (BID) dosing formulations in acute coronary syndrome (ACS) patients. Poster presented at: International Society Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, May 21-25, 2011, Baltimore, Maryland.	**Design:** Retrospective, claims-based cohort study using prescription claims and consumer insights (mortality) databases **Sample Size:** 3004 patients with newly diagnosed ACS Carvedilol once daily, n=168 Carvedilol twice daily, n=2086 Metformin once daily, n=136 Metformin twice daily, n=614 **Treatments:** Carvedilol once daily Carvedilol twice daily Metformin once daily Metformin twice daily	**Inclusion:** Patients who were newly diagnosed ACS patients aged ≥18 years during inpatient hospitalization; were dispensed a prescription for carvedilol and/or metformin within 60 days of discharge from ACS inpatient hospitalization; pharmacy activity for ≥1 year post-discharge or with a recorded post-discharge mortality; filled ≥2 prescriptions for the same drug and formulation (refill compliance analysis) **Exclusion:** Not reported	**Endpoints** **Persistency** 6 months • Carvedilol once daily: 44%; carvedilol twice daily: 43.7% (p=0.934) • Metformin once daily: 50.7%; metformin twice daily: 53.7% (p=0.524) 12 months • Carvedilol once daily: 24.4%; carvedilol twice daily: 25.5% (p=0.753) • Metformin once daily: 28.7%; metformin twice daily: 35.0% (p=0.158) **Days on therapy** 6 months • Carvedilol once daily: 120.5; carvedilol twice daily: 121.9 (p=0.766) • Metformin once daily: 123.6; metformin twice daily: 136.2 (p=0.526) 12 months • Carvedilol once daily: 196.7; carvedilol twice daily: 203.0 (p=0.526) • Metformin oncedaily: 206.1; metformin twice daily: 237.7 (p=0.005) **Average number of prescriptions** 6 months • Carvedilol once daily: 4.4; carvedilol twice daily: 4.6 (p=0.471) • Metformin once daily: 4.5; metformin twice daily: 5.4 (p=0.0002) 12 months • Carvedilol once daily: 7.0; carvedilol twice daily: 7.4 (p=0.356) • Metformin once daily: 7.2; metformin twice daily: 9.1 (p<0.0001) **Refill Compliance (MPR)** 12 months • Carvedilol once daily: 84.2%; carvedilol twice daily: 80.7% (p=0.026) • Metformin once daily: 77.6%; metformin twice daily:81.6% (p=0.066)

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Lu et al. *BMC Health Services Res*. 2008;8:75.	**Design:** Systematic literature review regarding interventions targeting drug use in the managed care setting **Sample size:** 51 methodologically adequate studies **Treatment:** N/A	**Inclusion:** Articles published between July 2001 and January 2007 with the relevant search terms (eg, managed care programs, health maintenance organizations, preferred provider organization) identified using MEDLINE and EMBASE; studies conducted in the US managed care setting that described intervention(s) targeting medication use, had adequate methodology with a comparison group of at least 20 subjects, and measured drug-related outcomes **Exclusion:** Clinical effectiveness trials, cost effectiveness studies, descriptive studies, and those examining vaccinations	**Endpoints** Finding Identified Regarding Effective Interventions: *Educational Interventions:* • Dissemination of educational materials alone is an ineffective intervention . • One-to-one outreach is effective at changing aspects of physician behavior, particularly medication use and may increase patient satisfaction. • Multifaceted interventions are more effective in changing medication use than interventions using a single intervention. *Monitoring and Feedback:* Monitoring and feedback approaches have small to moderate effects on medication use. *Formulary Interventions:* Tiered formulary and patient copayments reduce the use of nonpreferred drugs, reduce costs to the insurer and increase patient costs, as expected; however, these interventions may also be associated with increased rates of medication switching or discontinuation of cost-effective drugs. *Collaborative Care Involving Pharmacists:* Interventions found to improve the quality of care include coordination of pharmacist services as a component of patient care and disease management programs.
Consequences of Not Discontinuing Clopidogrel Use Prior to Surgery			
Berger et al. *J Am Coll Cardiol*. 2008;52: 1693-1701. Harshaw et al. Poster presented at: American Heart Association 9th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke; May 1-2, 2008; Baltimore, Maryland.	**Design:** Retrospective cohort analysis using case report forms completed using eligible patients' case records **Sample Size:** 596 patients from 14 hospitals **Treatments:** • Clopidogrel within 5 days of their CABG procedure (Group A) • Clopidogrel-naive or no treatment within 5 days of their CABG procedure (Group B)	**Inclusion:** Patients aged ≥30 years who presented with ACS and underwent CABG during the index hospitalization and for whom complete medical records were available **Exclusion:** Patients with end stage renal disease or a bleeding disorder, who received another open-heart procedures along with CABG, were lost to follow-up within 30 days after CABG surgery, whose cause of death was unrelated to cardiac condition or surgery, whose surgery was not performed within 7 days of the index hospitalization or angiography for ACS, who might have experienced cardiac rupture or were chronically using corticosteroids	**Primary** Rate of Reoperation: Group A: 19 (6.4%); Group B: 5 (1.7%); p=0.004 Major Bleeding: Group A: 71 (34.5%); Group B: 53 (25.6%); p=0.049 Inpatient LOS: Group A: 9.7 ±6.0 days; Group B: 8.6±4.7 days; p=0.016 **Secondary** Reoperation for Bleeding Complication: Group A: 14 (4.7%); Group B: 4 (1.3%); p=0.017 CURE Major Bleeding: Group A: 113 (53.8%); Group B: 73 (34.9%); p<0.001 TIMI Major Bleeding: Group A: 114 (54.3%); Group B: 98 (46.9%); p=0.130 Non-life–threatening Bleeding: Group A: 56 (18.8%); Group B: 55 (18.5%) p=0.916

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
			In-hospital Death: Group A: 4 (1.3%); Group B: 1 (0.3%); p=0.373 Death/Reinfarction/Stroke: Group A: 8 (2.7%); Group B: 5 (1.7%); p=0.400 Transfusion Received (Mean Units): Group A: 4.90±7.90; Group B: 2.03±3.75; p<0.001 Hospital Readmission Within 30 Days: Group A: 27 (9.1%); Group B: 24 (8.1%); p=0.670 Post-surgical LOS: Group A: 7.2 ±5.53; Group B: 6.3±3.87; p=0.054 ICU LOS: Group A: 2.7±3.17; Group B: 2.4±2.52; p=0.059 **Pharmacoeconomic Subanalysis** Total Costs: Group A: $28,602 ($9,320-$136,101); Group B: $25,442 ($8,331-$131,806); p=0.004 Direct Costs: Group A: $18,969 ($6,467-$97,067); Group B: $17,831 ($4,598-$93,309); p=0.017 Overhead Costs: Group A: $11,106 ($4,453-$51,446); Group B: $10,148 ($3,733-$48,881); p=0.006

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Pickard et al. *Pharmacotherapy*. 2008;28:376-392.	**Design:** Literature review using relevant key words in MEDLINE and EMBASE; the Cochrane Database for Systematic Reviews was also searched **Sample size:** 23 studies (Data included 3505 patients) **Treatment:** Clopidogrel within 7 days of undergoing a CABG procedure	**Inclusion:** Randomized controlled trials, prospective observational studies or retrospective studies from January 1, 1990, to April 30, 2007, analyzing characteristics and outcomes of patients exposed to clopidogrel within 7 days of CABG surgery and reporting postoperative bleeding-related outcomes **Exclusion:** Reviews, case reports, editorials, letters, or any other nonoriginal research article or if the sample size assessed was <20 patients	**Endpoints** Patients exposed to clopidogrel within 7 days of their CABG procedure have poorer outcomes than those not exposed within 7 days of surgery. Related Complications: Patients exposed to clopidogrel were found to have significantly higher chest tube output vs patients not exposed to clopidogrel in 4 of 7 studies comparing this endpoint. Transfusion Requirements: Clopidogrel exposed patients were found to require significantly greater platelet transfusions in 10 of the 11 studies that assessed this endpoint; these patients were also associated with a trend towards higher rates of reoperation due to uncontrolled bleeding and/or cardiac tamponade. Resource Utilization: Most studies did not find a significant difference in resource utilization-related outcomes based on clopidogrel exposure.
Ho et al. *JAMA*. 2008:299:532-539.	**Design:** Retrospective cohort study **Sample size:** 3,137 patients **Treatment:** Clopidogrel following hospitalization • Medically treated cohort (n=1568) • PCI-treated patients (n=1569)	**Inclusion:** Patients discharged from 1 of the 127 VA hospitals between October 1, 2003, and March 31, 2005, with acute MI or UA with clopidogrel treatment who remained event-free **Exclusion:** Patients who had an AE while receiving clopidogrel therapy or those transferred into VA hospital from other medical facilities	**Primary** Combination of All-cause Mortality or Acute MI Hospitalization Following Cessation of Clopidogrel Therapy: • A total of 268 (17.1%) patients in the medically treated cohort died (n=155) or experienced an acute MI (n=113). • The majority (60.8%; n=163) of these events occurred within 90 days of cessation of therapy, whereas 21.3% (n=57) occurred during 91 to 180 days and 9.7% (n=26) occurred during 181 to 270 days after stopping treatment with clopidogrel. • A total of 124 (7.9%) patients in the PCI-treated cohort died (n=68) or experienced an acute MI (n=56). • The majority (58.9%; n=73) of these events occurred within 90 days of cessation of therapy, whereas 23.4% (n=29) occurred during 91 to 180 days and 6.5% (n=8) occurred during 181 to 270 days after stopping treatment with clopidogrel. **Secondary** Incidence and Timing of AEs Following Cessation of Clopidogrel Therapy: • Medically treated cohort: the 90-day period following cessation of clopidogrel therapy was associated with a significantly greater risk of AEs than was the 91- to 180-day period (IRR, 1.98; 95% CI 1.46, 2.69), supporting the presence of a potential rebound effect following the cessation of clopidogrel. • PCI-treated cohort: the 90-day period following cessation of clopidogrel therapy was associated with a significantly greater risk of AEs than was the 91- to 180-day period (IRR, 1.82; 95% CI 1.17, 2.83).

Citation	Design/Sample Size /Treatments	Inclusion/ Exclusion Criteria	Results
Genetic Nonresponders to Clopidogrel and Associated Outcomes			
Crespin et al. Presented at: Personalized Medicine: Two Papers on The Cost Effectiveness of Genetic Tests for Determining Treatment for Patients With Acute Coronary Syndromes (ACS) Seminar; June 18, 2010: Chapel Hill, North Carolina.	**Design:** A decision tree/Markov model was developed to compare the cost effectiveness of genotype-driven administration of clopidogrel versus universal prescribing of ticagrelor in Medicare patients (66 years) with ACS **Sample size:** N/A **Treatment:** • Patients receive CYP2C19*2 mutation testing and either receive ticagrelor (if mutation present) or clopidogrel (if mutation not present) • Patients all treated with ticagrelor without genetic testing	**Inclusion:** Medicare patients 66 years of age with ACS **Exclusion:** N/A	**QALYs Gained for Universal Ticagrelor vs. Genotype-driven Strategy:** • After 1 year: 0.01 • After 5 years: 0.06 • After 30 years: 0.14 **ICER ($/QALY) for Universal Ticagrelor vs. Genotype-driven Strategy:** • After 1 year: $103,600 • After 5 years: $17,448 • After 30 years: $9161 **Probabilistic Sensitivity Analysis:** Universal ticagrelor treatment strategy remained below $50,000/QALY in 97.4% of simulations. **Cost-effectiveness Acceptability Curve:** The cost-effectiveness acceptability curve indicated a 95% probability that universal ticagrelor is cost-effective compared with the genotype-driven strategy, given a maximum willingness to pay of $32,840.

Key: ACS = acute coronary syndrome; AEs = adverse events; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CI = confidence interval; CPT = Current Procedural Terminology; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; ER = emergency room; HFHS = Henry Ford Health System; HPR = high platelet reactivity; HR = hazard ratio; ICD-9 = *International Classification of Diseases, 9th Edition/Revision*; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; IHD = ischemic heart disease; IRR = incidence rate ratios; LOS = length of stay; MCO = managed care organization; MI = myocardial infarction; N/A = not applicable; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; QALY = quality-adjusted life year; TIMI: Thrombolysis in Myocardial Infarction; UA = unstable angina; VA = Veterans Affairs.

SECTION 6.0 Supporting Information

6.1 BRILINTA PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA™ (ticagrelor) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

----------INDICATIONS AND USAGE----------

BRILINTA is a P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily. (1, 5.2, 14)

----------DOSAGE AND ADMINISTRATION--------

- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

--------DOSAGE FORMS AND STRENGTHS---------

- 90 mg tablets (3)

----------CONTRAINDICATIONS----------

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)

----------WARNINGS AND PRECAUTIONS---------

- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS ----------

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

See 17 For PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

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- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

1 INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis *[see Clinical Studies (14)]*.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily.

After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population *[see Clinical Studies (14)]*.

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.3 Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased *[see Adverse Reactions (6.1)]*.

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

5.2 Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg *[see Dosage and Administration (2) and Clinical Studies (14)]*.

5.3 Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

5.5 Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

5.6 Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.7 Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea *[see Warnings and Precautions (5.4)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

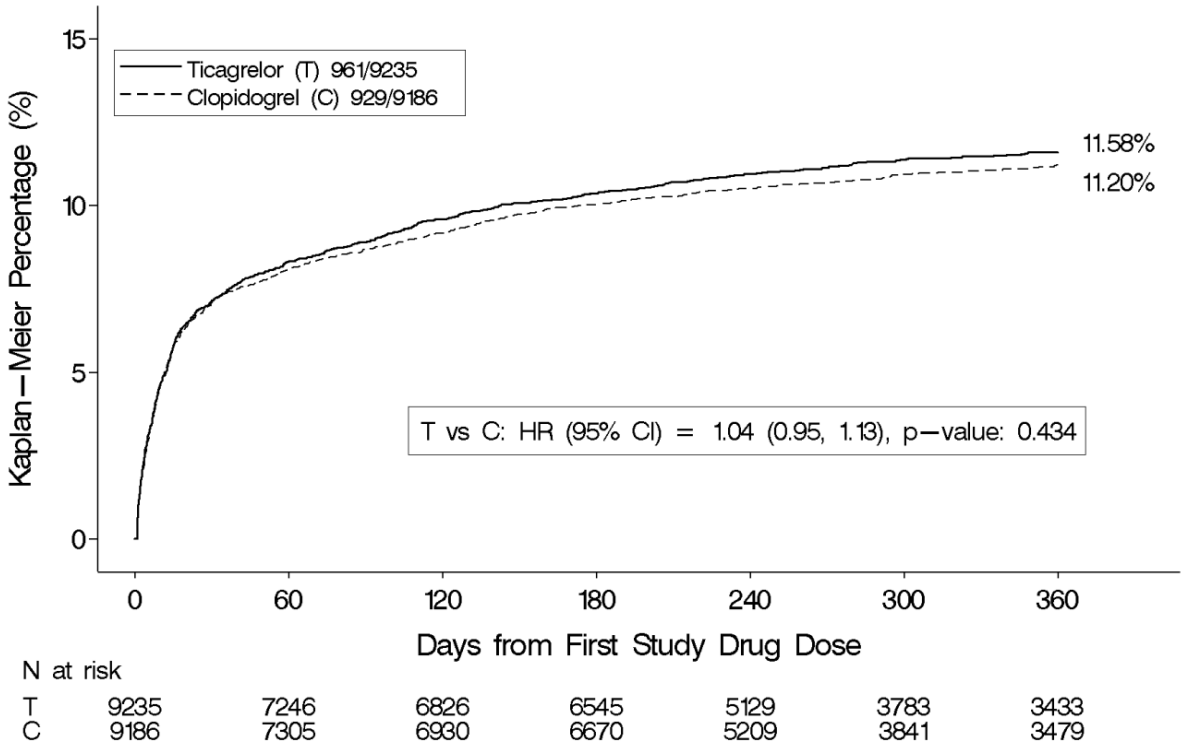
BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding
PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 - Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 - Non-CABG related bleeds (KM%)

	BRILINTA N=9235	**Clopidogrel N=9186**
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 – CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	**Clopidogrel N=814**
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 – Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	**Clopidogrel N=9186**
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a]Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference

disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:
In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

7 DRUG INTERACTIONS

Effects of other drugs
Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

7.1 CYP3A inhibitors

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

7.2 CYP3A inducers

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

Effect of BRILINTA on other drugs
Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

7.4 Simvastatin, lovastatin

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg *[see Clinical Pharmacology (12.3)]*.

7.5 Digoxin

Digoxin: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy *[see Clinical Pharmacology (12.3)]*.

7.6 Other Concomitant Therapy

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied *[see Clinical Pharmacology (12.3)]*.

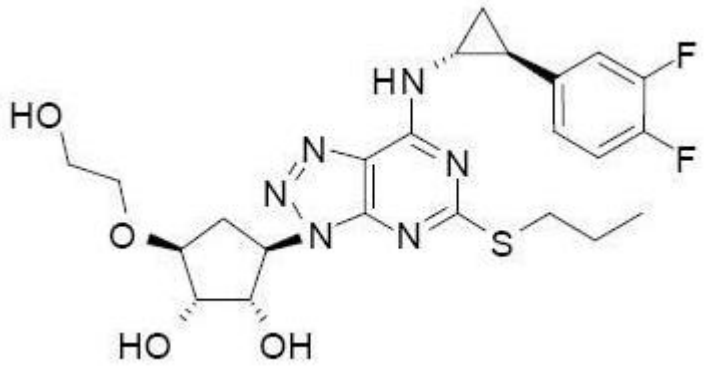
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Figure 2 - Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

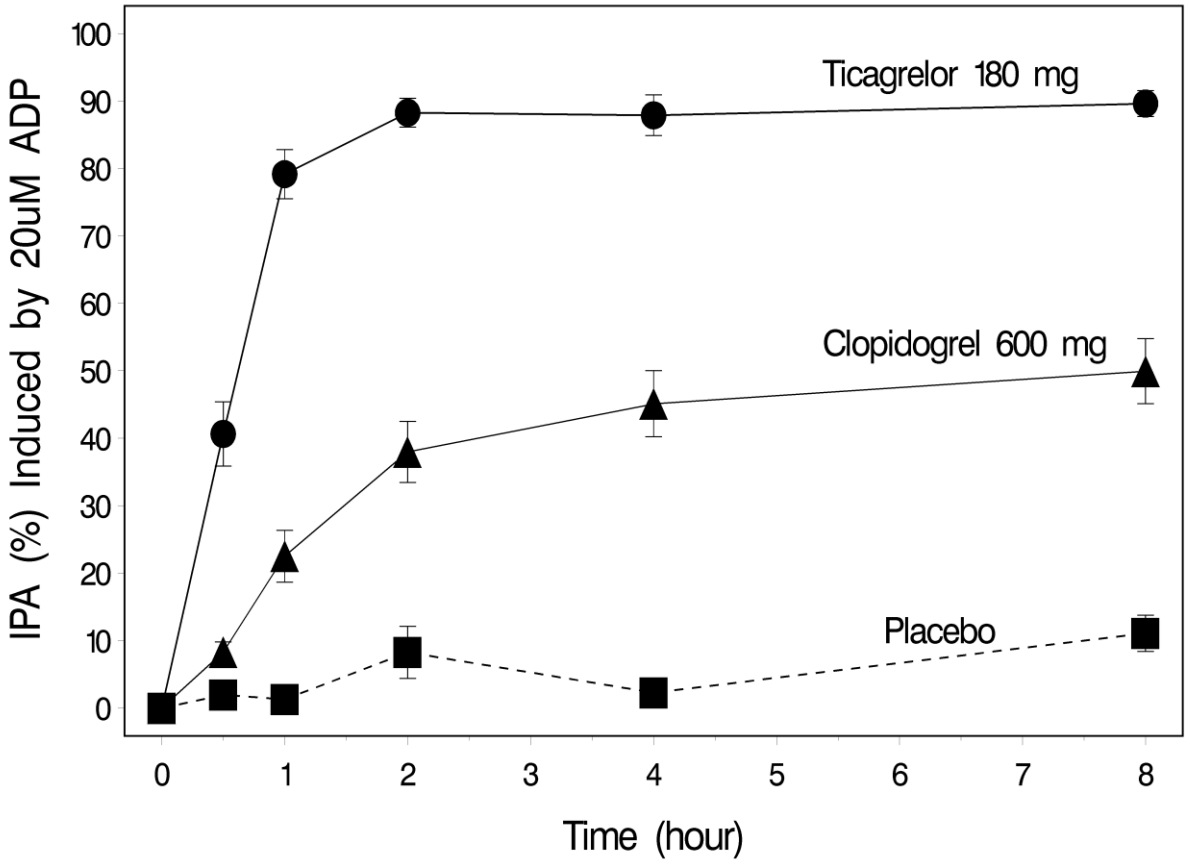
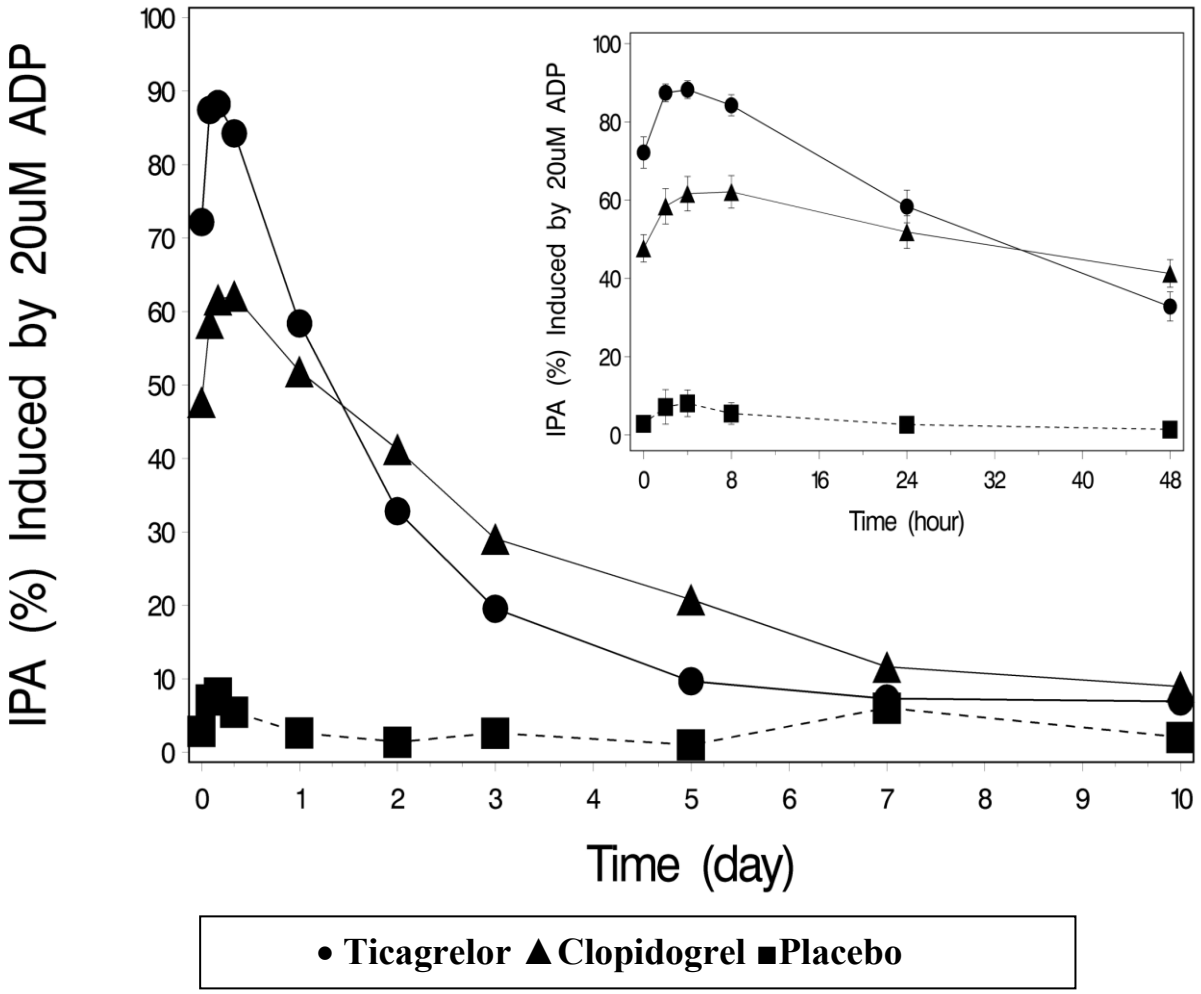


Figure 3 - Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

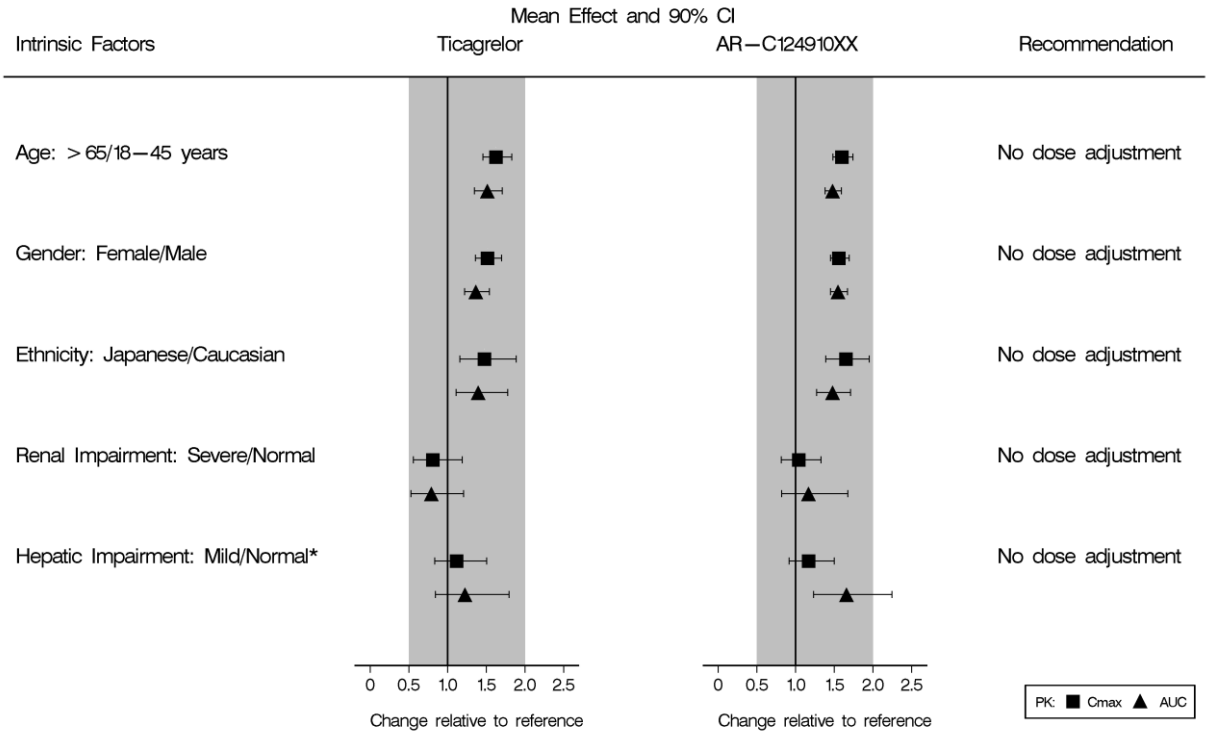
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

Figure 4 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor



*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

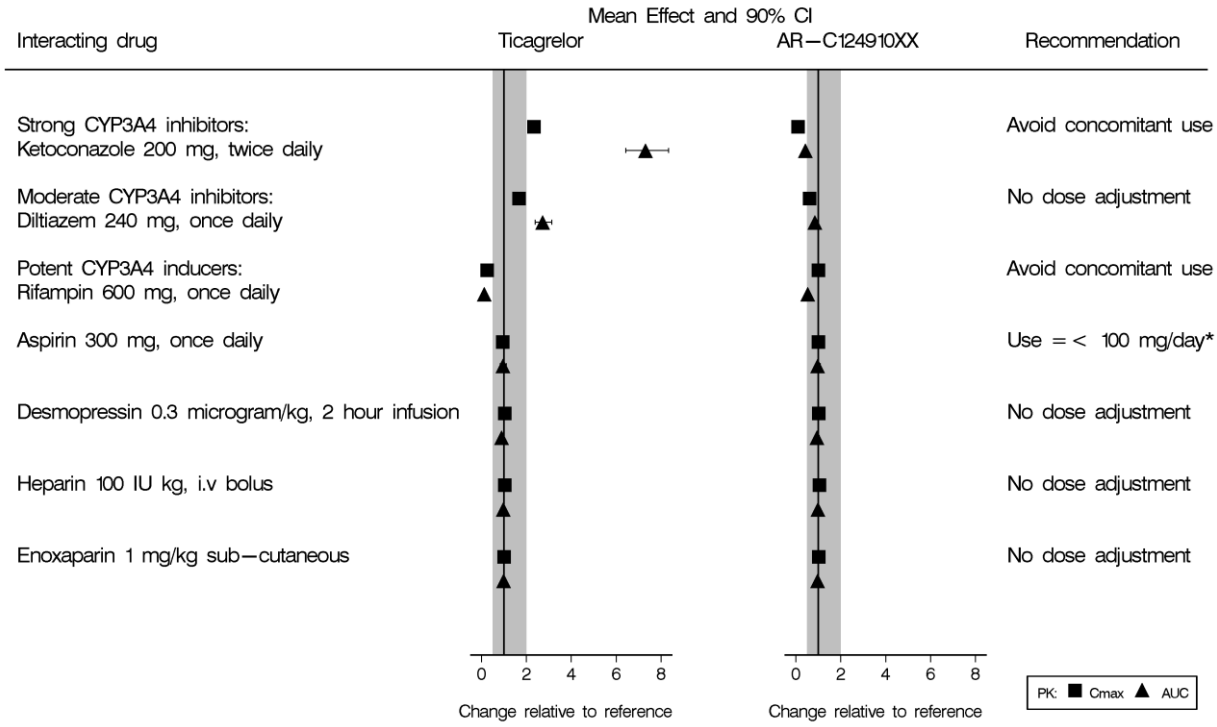
Pediatric
Ticagrelor has not been evaluated in a pediatric population *[see Use in Specific Populations (8.4)]*.

Body Weight
No dose adjustment is necessary for ticagrelor based on weight.

Smoking
Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Figure 5 – Effect of co-administered drugs on the pharmacokinetics of ticagrelor

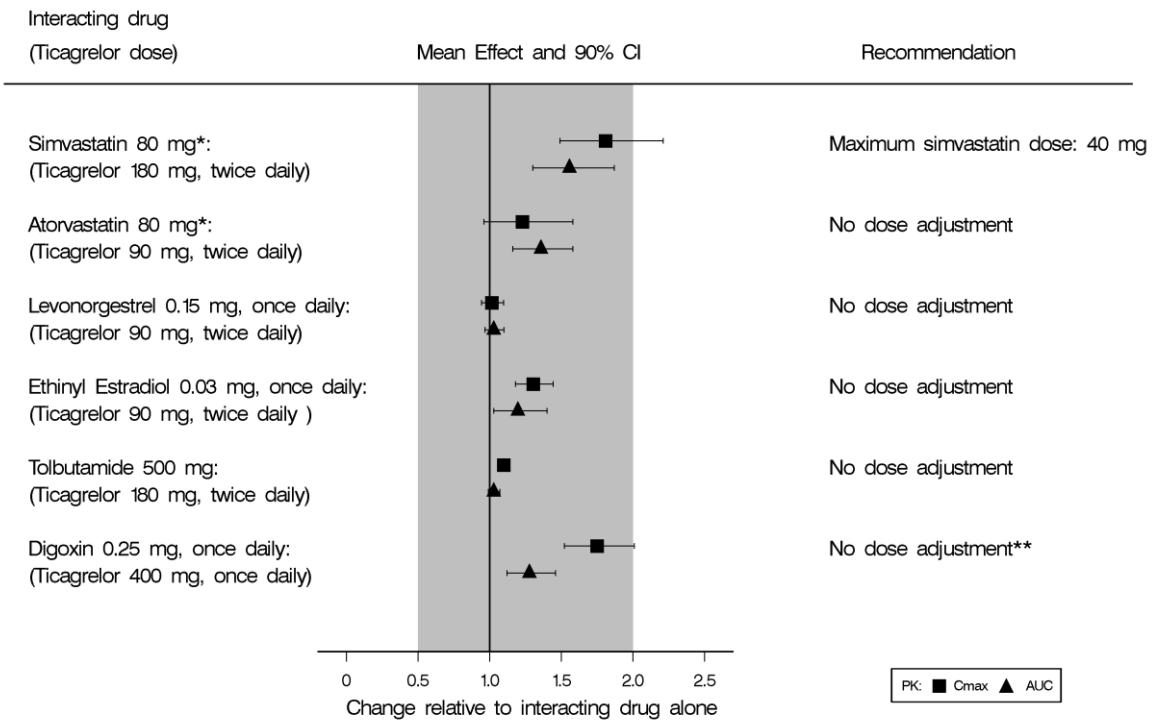


*See *Dosage and Administration (2).*

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

Figure 6 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC).

Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Because of ticagrelor's metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

Table 4 – Patients with Outcome Events, in PLATO (KM%)

	BRILINTA N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints [a]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[b]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[b]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

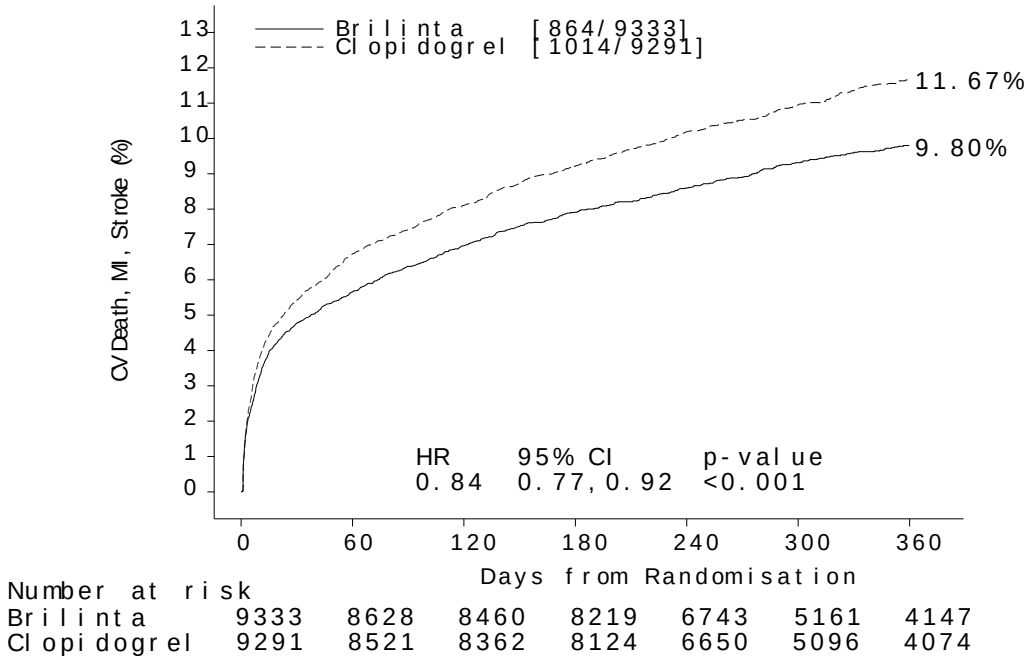
[a] First occurrence of specified event at any time
[b]Includes patients that could have had other non-fatal events or died

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

Figure 7 – Time to First Occurrence of CV death, MI, or Stroke in PLATO

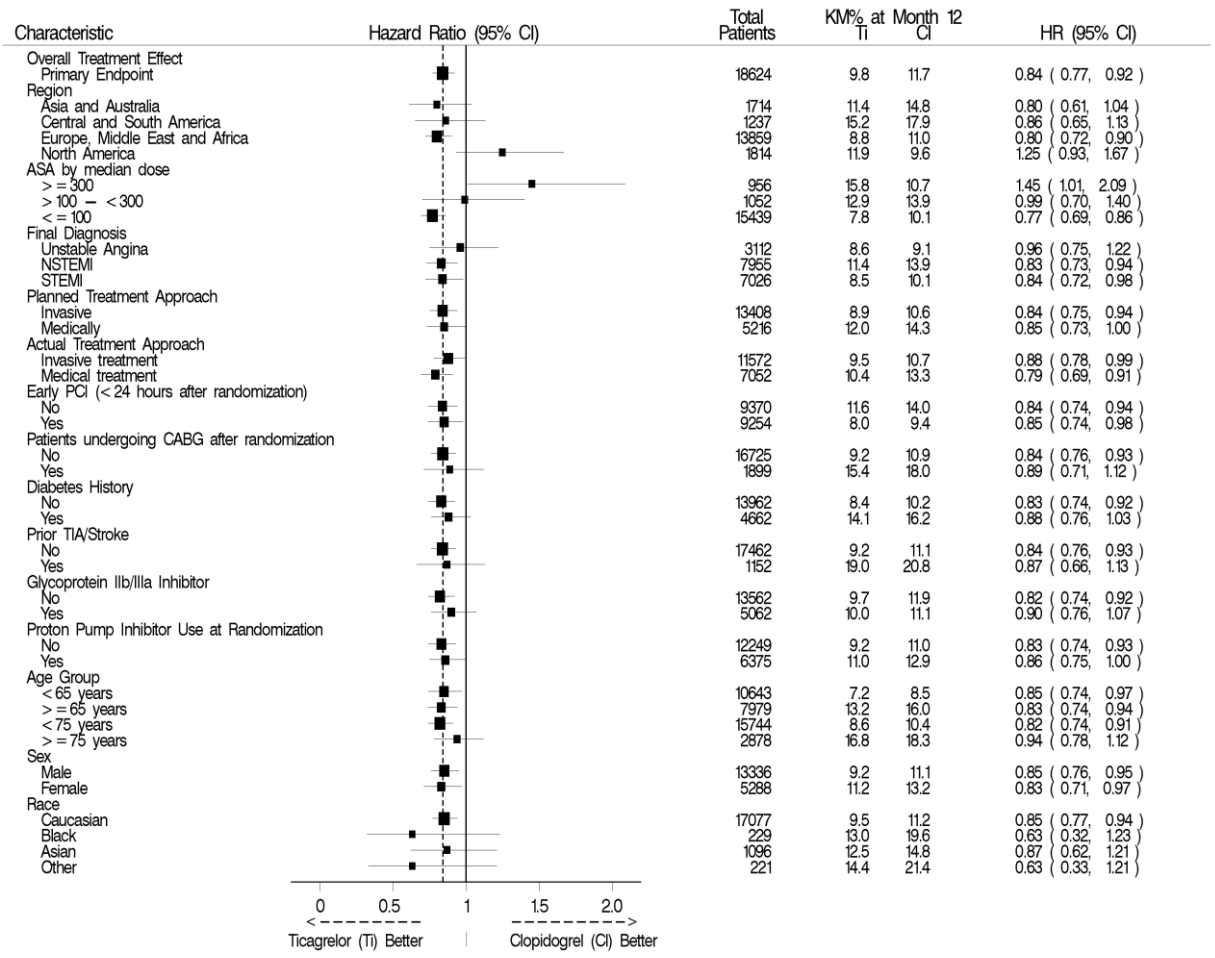


The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Figure 8 – Subgroup analyses of PLATO



Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

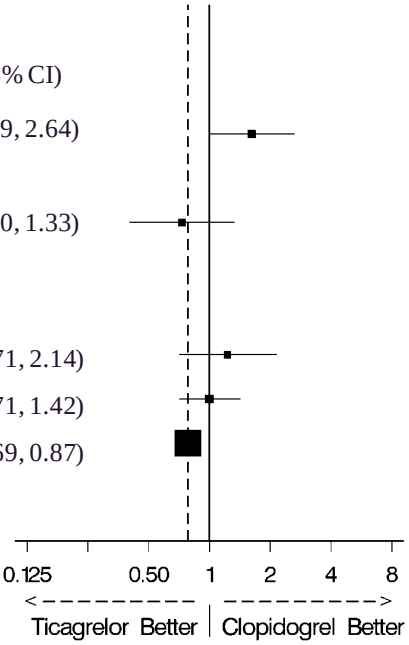
Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg

and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤ 100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by region and dose.

Table 5 – PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US

		Ticagrelor		Clopidogrel		
Region	ASA Dose (mg)	N	Events	N	Events	HR (95% CI)
US	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100-<300	22	2	16	2	-
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100-<300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)



Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics

In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

Bottles of 60 – NDC 0186-0777-60

Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

- Tell patients to take BRILINTA exactly as prescribed.
- Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
- Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
- Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:

- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).

Issued: July 20, 2011

Manufactured by: AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

MEDICATION GUIDE

BRILINTA ™ (brih-LIN-tah)
(ticagrelor)
Tablets

Read this Medication Guide before you start taking BRILINTA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about BRILINTA?

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke **but BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death.** In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like "coffee grounds"
- red or black stools (looks like tar)
- coughing up blood or blood clots

Do not stop taking BRILINTA without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

Taking BRILINTA with aspirin
BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

What is BRILINTA?

BRILINTA is a prescription medicine used to treat people who:

- have had a recent heart attack or severe chest pain that happened because their heart was not getting enough oxygen.
- have had a heart attack or chest pain and are being treated with medicines or with a procedure to open blocked arteries in the heart.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal.

Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and works in children.

Who should not take BRILINTA?

Do not take BRILINTA if you:

- are bleeding now
- have a history of bleeding in the brain
- have bleeding from your stomach or intestine now (an ulcer)
- have severe liver problems

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

What should I tell my doctor before taking BRILINTA?

Before you take BRILINTA, tell your doctor if you:

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant, or are plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor should decide if you will take BRILINTA.
- are breastfeeding. It is not known if BRILINTA passes into your breast-milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking BRILINTA. They should talk to the doctor who prescribed BRILINTA for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. **BRILINTA may**

affect the way other medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:
- an HIV-AIDS medicine
- medicine for heart conditions or high blood pressure
- medicine for high blood cholesterol levels
- an anti-fungal medicine by mouth
- an anti-seizure medicine
- a blood thinner medicine
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BRILINTA?

- Take BRILINTA exactly as prescribed by your doctor.
- Your doctor will tell you how many BRILINTA tablets to take and when to take them.
- Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
- Take your doses of BRILINTA around the same time every day.
- If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take two doses at the same time unless your doctor tells you to.
- If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

What are the possible side effects of BRILINTA?

BRILINTA can cause serious side effects, including:

- **See "What is the most important information I should know about BRILINTA?"**
- **Shortness of breath.** Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of BRILINTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BRILINTA?

- Store BRILINTA at room temperature between 59°F to 86°F (15°C to 30°C).

Keep BRILINTA and all medicines out of the reach of children.

General information about BRILINTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRILINTA for a condition for which it was not prescribed. Do not give BRILINTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about BRILINTA. If you would like more information about BRILINTA, talk with your doctor. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

For more information call 1-800-236-9933 or go to www.Brilinta.com.

What are the ingredients in BRILINTA?

Active ingredient: ticagrelor

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

Issued: 07/2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

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6.3 ECONOMIC MODEL

An economic model is not available for distribution.